

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

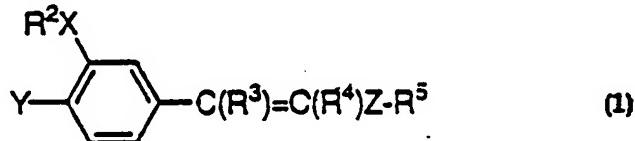
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ :		(11) International Publication Number:	WO 94/20455
C07C 255/36, A61K 31/275, 31/33, C07D 213/57, 213/61, 333/24, 213/30, 233/26, 237/14, 237/24, 239/10, 241/18		A1	(43) International Publication Date: 15 September 1994 (15.09.94)
(21) International Application Number:		PCT/GB94/00452.	
(22) International Filing Date:		9 March 1994 (09.03.94)	
(30) Priority Data:		93049195 10 March 1993 (10.03.93) GB	
(71) Applicant:		CELLTECH LIMITED [GB/GB]; 216 Bath Road, Slough, Berkshire SL1 4EN (GB).	
(72) Inventors:		WARRELOW, Graham, John; Oakside, 4 Wieland Road, Northwood, Middlesex HA6 3QU (GB). COLE, Valerie, Anne; 66 Chiltern Road, Burnham, Buckinghamshire SL1 7NH (GB). ALEXANDER, Rikki, Peter; 14 Carrington Road, High Wycombe, Buckinghamshire HP12 3HY (GB).	
(74) Agent:		SKAILES, Humphrey, J.; Frank B. Dein & Co., Imperial House, 15-19 Kingsway, London WC2B 6UZ (GB).	
(31) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).			
Published <i>With international search report.</i>			

(54) Title: STYRYL DERIVATIVES, THEIR PREPARATION AND USE AS PDE-IV INHIBITORS

(57) Abstract

Compounds of general formula (1) are described wherein Y is a halogen atom or a group -OR¹, wherein R¹ is an optionally substituted alkyl group; X is -O-, -S-, or



-N(R⁶), wherein R⁶ is a hydrogen atom or an optionally substituted alkyl group; R² is an optionally substituted cycloalkyl or cycloalkenyl group; R³ and R⁴, which may be the same or different, is each a hydrogen atom or an optionally substituted alkyl, -CO₂R⁷ (wherein R⁷ is a hydrogen atom, an optionally substituted alkyl, aralkyl, aryl, aryloxyalkyl, alkanoyloxyalkyl or aroyloxyalkyl group), -CONR⁸R⁹ (where R⁸ and R⁹, which may be the same or different, is as defined for R³), -CSNR⁸R⁹, -CN or -CH₂CN group; Z is -(CH₂)_n where n is zero or an integer 1, 2 or 3; R⁵ is an optionally substituted monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms; and the salts, solvates, hydrates, prodrugs and N-oxides thereof. Compounds according to the invention are potent and selective phosphodiesterase type IV inhibitors and are useful in the prophylaxis and treatment of diseases such as asthma where an unwanted inflammatory response or muscular spasm is present.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australis	GE	Georgia	MW	Malawi
BB	Barbados	GN	Greece	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	ID	Iceland	NZ	New Zealand
BJ	Beira	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LK	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CJ	Czechoslovakia	LV	Latvia	TG	Togo
CI	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

STYRYL DERIVATIVES, THEIR PREPARATION AND USE AS PDE-IV INHIBITORS

5 This invention relates to a novel series of styryl derivatives, to processes for their preparation, to pharmaceutical compositions containing them, and to their use in medicine.

10 Many hormones and neurotransmitters modulate tissue function by elevating intra-cellular levels of adenosine 3', 5'-cyclic monophosphate (cAMP). The cellular levels of cAMP are regulated by mechanisms which control synthesis and breakdown. The synthesis of cAMP is controlled by adenylyl cyclase which may be directly activated by agents such as forskolin or indirectly activated by the binding of specific agonists to cell
15 surface receptors which are coupled to adenylyl cyclase. The breakdown of cAMP is controlled by a family of phosphodiesterase (PDE) isoenzymes, which also control the breakdown of guanosine 3',5'-cyclic monophosphate (cGMP). To date, seven members of the family have been described (PDE I-VII) the distribution of which varies from tissue to
20 tissue. This suggests that specific inhibitors of PDE isoenzymes could achieve differential elevation of cAMP in different tissues. [for reviews of PDE distribution, structure, function and regulation, see Beavo & Reifsnyder (1990) TIPS, 11: 150-155 and Nicholson et al (1991) TIPS, 12: 19-27].

25

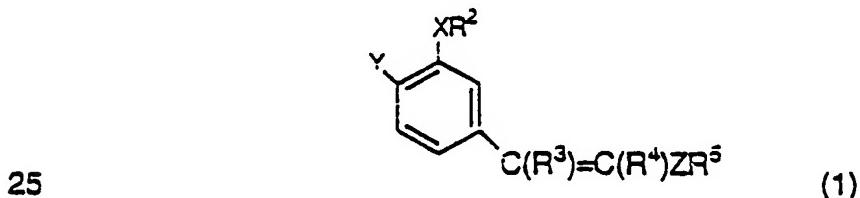
There is clear evidence that elevation of cAMP in inflammatory leukocytes leads to inhibition of their activation. Furthermore, elevation of cAMP in airway smooth muscle has a spasmolytic effect. In these tissues, PDE IV plays a major role in the hydrolysis of cAMP. It can be expected, therefore, that selective inhibitors of PDE IV would have therapeutic effects in inflammatory diseases such as asthma, by achieving both anti-inflammatory and bronchodilator effects.

30
35 The design of PDE IV inhibitors has met with limited success to date, in that many of the potential PDE IV inhibitors which have been synthesised have lacked potency and/or have been capable of inhibiting more than one

type of PDE isoenzyme in a non-selective manner. Lack of a selective action has been a particular problem given the widespread role of cAMP *in vivo* and what is needed are potent selective PDE IV inhibitors with an inhibitory action against PDE IV and little or no action against other PDE isoenzymes.

We have now found a novel series of styryl derivatives, members of which, compared to known structurally similar compounds, are potent inhibitors of PDE IV at concentrations at which they have little or no inhibitory action on other PDE isoenzymes. These compounds inhibit human recombinant PDE IV enzyme and also elevate cAMP in isolated leukocytes. Certain compounds prevent inflammation in the lungs induced by carrageenan, platelet-activating factor (PAF), interleukin-5 (IL-5) or antigen challenge. These compounds also suppress the hyperresponsiveness of airway smooth muscle seen in inflamed lungs. Advantageously, compounds according to the invention have good oral activity and at orally effective doses exhibit little or none of the side-effects associated with known PDE IV inhibitors, such as rolipram. The compounds of the invention are therefore of use in medicine, especially in the prophylaxis and treatment of asthma.

Thus according to one aspect of the invention, we provide a compound of formula (1)



wherein

- Y is a halogen atom or a group -OR¹, where R¹ is an optionally substituted alkyl group;
- 30 X is -O-, -S-, or -N(R⁶)-, where R⁶ is a hydrogen atom or an optionally substituted alkyl group;
- R² is an optionally substituted cycloalkyl or cycloalkenyl group;

- R³ and R⁴, which may be the same or different, is each a hydrogen atom or an optionally substituted alkyl, -CO₂R⁷ (where R⁷ is a hydrogen atom, or an optionally substituted alkyl, aralkyl or aryl group), -CONR⁸R⁹ (where R⁸ and R⁹ which may be the same or different is as described for R⁷), 5 -CSNR⁸R⁹, -CN or -CH₂CN group;
- Z is -(CH₂)_n- where n is zero or an integer 1, 2 or 3;
- R⁵ is an optionally substituted monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms;
- 10 and the salts, solvates, hydrates, prodrugs and N-oxides thereof.

The compounds of formula (1) exist as geometrical isomers, and the invention extends to all such individual isomers and mixtures thereof. Formula (1) and the formulae hereinafter should be understood to include 15 all individual isomers and mixtures thereof, unless stated otherwise, and even though only one isomer may be depicted.

- In the compounds of formula (1), when Y is a halogen atom it may be for example a fluorine, chlorine, bromine or iodine atom.
- 20 When Y in the compounds of formula (1) is a group -OR¹. R¹ may be, for example, an optionally substituted straight or branched C₁-3-alkyl group, such as a methyl, ethyl, n-propyl, or i-propyl groups. Optional substituents which may be present on R¹ groups include one or more 25 halogen atoms, e.g. fluorine, or chlorine atoms.

- When X in compounds of formula (1) is a -N(R⁶)- group it may be a -NH-group or a group -N(R⁶)- where R⁶ is an optionally substituted C₁-6 alkyl group such as a methyl or ethyl group.
- 30 When R² in the compounds of formula (1) is an optionally substituted cycloalkyl or cycloalkenyl group it may be for example a C₃-8cycloalkyl group such as a cyclobutyl, cyclopentyl or cyclohexyl group or a C₃-8 cycloalkenyl group containing for example one or two double bonds such as a 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2,4-35 cyclopentadien-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl, 2,4-

cyclohexadien-1-yl or 3,5-cyclonexadien-1-yl group, each cycloalkyl or cycloalkenyl group being optionally substituted by one, two or three substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, straight or branched C₁-C₆alkyl e.g. C₁-C₃alkyl such as 5 methyl or ethyl, hydroxyl or C₁-C₆alkoxy e.g. C₁-C₃alkoxy such as methoxy or ethoxy groups.

Alkyl groups represented by R³ and R⁴ in compounds of formula (1) include optionally substituted straight or branched C₁-C₆ alkyl groups for 10 example C₁-C₃ alkyl groups, such as methyl, ethyl n-propyl or i-propyl groups. Optional substituents which may be present on R³ or R⁴ include one or more halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl or C₁-C₆ alkoxy e.g. C₁-C₃ alkoxy such as methoxy or ethoxy groups, or thiol or C₁-C₆ alkylthio e.g. C₁-C₃ alkythio such as 15 methylthio or ethylthio groups. Particular examples of R³ or R⁴ alkyl groups include -CH₃, -CH₂CH₃, -CH₂OH, -CH₂Cl, -CH₂F, -CHCl₂, -CHF₂ and -CH₂OCH₃ groups.

When R³ and/or R⁴ is a -CO₂R⁷, -CONR⁸R⁹ or -CSNR⁸R⁹ group it may be 20 for example a -CO₂H, -CONH₂, or -CSNH₂ group, or a group -CO₂R⁷, -CONR⁸R⁹, -CSNR⁸R⁹, -CONHR⁹, or -CSNHR⁹ wherein R⁷, R⁸ and R⁹ where present is a C₁-C₃ alkyl group such as a methyl or ethyl group, a C₆-25 12 aryl group, for example an optionally substituted phenyl, or a 1- or 2-naphthyl group, or a C₆-12 arylC₁-C₃ alkyl group such as an optionally substituted benzyl or phenethyl group. Optional substituents which may be present on these groups include R¹⁰ substituents discussed below in relation to the group R⁵.

In the compounds of formula (1) Z may represent a bond connecting the 30 group R⁵ to the rest of the molecule, or represents a group -CH₂-, -(CH₂)₂- or -(CH₂)₃-.

Monocyclic or bicyclic aryl groups represented by the group R⁵ in 35 compounds of formula (1) include for example C₆-12 optionally substituted aryl groups, for example optionally substituted phenyl, 1- or 2-naphthyl, indenyl or isoindenyl groups.

- When the monocyclic or bicyclic aryl group contains one or more heteroatoms it may be a C₁₋₉ for example a C₃₋₉, optionally substituted heteroaryl group containing for example one, two, three or more heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, heteroaryl groups may be for example monocyclic or bicyclic heteroaryl groups. Monocyclic heteroaryl groups include for example five- or six-membered heteroaryl groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms.
- 10 Examples of heteroaryl groups represented by R⁵ include pyrrolyl, furyl, thienyl, imidazolyl, N-methylimidazolyl, N-ethylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 15 pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, isobenzofuryl, benzothienyl, isobenzothienyl, indolyl, isoindolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, quinazolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl and 5,6,7,8-tetrahydroisoquinolinyl.
- 20 The heteroaryl group represented by R⁵ may be attached to the remainder of the molecule of formula (1) through any ring carbon or heteroatom as appropriate. Thus, for example, when the heteroaryl group is a pyridyl group it may be a 2-pyridyl, 3-pyridyl or 4-pyridyl group. When it is a thienyl group it may be a 2-thienyl or 3-thienyl group, and, similarly, when it is a furyl group it may be a 2-furyl or 3-furyl group. When it is a pyridazinyl group it may be a 3- or 4-pyridazinyl group, and when it is an imidazolyl group it may be a 1-, 2-, 4- or 5-imidazolyl group.
- 25 30 When in compounds of formula (1) the heteroaryl group is a nitrogen-containing heterocycle it may be possible to form quaternary salts, for example N-alkyl quaternary salts and the invention is to be understood to extend to such salts. Thus for example when the heteroaryl group is a pyridyl group, pyridinium salts may be formed, for example N-alkylpyridinium salts such as N-methyipyridinium.
- 35

The aryl or heteroaryl groups represented by R⁵ in compounds of formula (1) may each optionally be substituted by one, two, three or more substituents [R¹⁰]. The substituent R¹⁰ may be selected from an atom or group R¹¹ or -Alk¹(R¹¹)_m wherein R¹¹ is a halogen atom, or an amino (-NH₂), substituted amino, nitro, cyano, hydroxyl (-OH), substituted hydroxyl, cycloalkoxy, formyl [HC(O)-], carboxyl (-CO₂H), esterified carboxyl, thiol (-SH), substituted thiol, -C(O)R^{7a} [where R^{7a} is as defined above for R⁷], -SO₃H, -SO₂R^{7a}, -SO₂N[R^{7a}R^{8a}], (where R^{8a} is as defined for R^{7a} and may be the same as or different to R^{7a}), -CON[R^{7a}R^{8a}], -NHSO₂R^{7a}, -N[SO₂R^{7a}]₂, -NHSO₂N[R^{7a}R^{8a}], -NHC(O)R^{7a}, or -NHC(O)OR^{7a} group; Alk¹ is a straight or branched C₁-alkylene, C₂-alkenylene, or C₂-alkynylene chain optionally interrupted by one, two, or three -O-, or -S- atoms or -S(O)p-, [where p is an integer 1 or 2] or -N(R⁶)- groups; and m is zero or an integer 1, 2 or 3.

When in the group -Alk¹(R¹¹)_m m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R¹¹ may be present on any suitable carbon atom in -Alk¹. Where more than one R¹¹ substituent is present these may be the same or different and may be present on the same or different carbon atom in Alk¹. Clearly, when m is zero and no substituent R¹¹ is present the alkylene, alkenylene or alkynylene chain represented by Alk¹ becomes an alkyl, alkenyl or alkynyl group.

25. When R¹¹ is a substituted amino group it may be a group -NH[Alk¹(R¹²)_m] [where Alk¹ and m are as defined above and R¹² is as defined above for R¹¹ but is not a substituted amino, a substituted hydroxyl or a substituted thiol group] or a group -N[Alk¹(R¹²)_m]₂ wherein each -Alk¹(R¹²)_m group is the same or different.

30. When R¹¹ is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

35. When R¹¹ is a cycloalkoxy group it may be for example a C₅-₇cycloalkoxy group such as a cyclopentyloxy or cyclohexyloxy group.

When R¹¹ is a substituted hydroxyl or substituted thiol group it may be a group -OAlk¹(R¹²)_m or -SAlk¹(R¹²)_m respectively, where Alk¹, R¹² and m are as just defined.

5

Esterified carboxyl groups represented by the group R¹¹ include groups of formula -CO₂Alk² wherein Alk² is a straight or branched, optionally substituted C₁-8alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C₆-12arylC₁-8alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C₆-12aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C₆-12 aryloxyC₁-8alkyl group such as an optionally substituted phenoxyethyl, phenoxyethyl, 1-naphthoxyethyl, or 2-naphthoxyethyl group; an optionally substituted C₁-8alkanoyloxyC₁-8alkyl group, such as a pivaloyloxyethyl, propionyloxyethyl or propionyloxypropyl group; or a C₆-12aroyloxyC₁-8alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk² group include R¹⁰ substituents described above.

20

When Alk¹ is present in or as a substituent R¹⁰ it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butynylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, -S(O)₂- or -N(R⁶)- groups.

30

Particularly useful atoms or groups represented by R¹⁰ include fluorine, chlorine, bromine or iodine atoms; or C₁-6alkyl, e.g. methyl or ethyl, C₁-6alkylamino, e.g. methylamino or ethylamino, C₁-6 hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, C₁-6alkylthiol e.g. methylthiol or ethylthiol, C₁-6alkoxy, e.g. methoxy or ethoxy, C₅-7cycloalkoxy, e.g. cyclopentyloxy, haloC₁-6alkyl, e.g. trifluoromethyl, C₁-6alkylamino, e.g. methylamino or ethylamino, amino (-NH₂), aminoC₁-6alkyl, e.g. aminomethyl or aminoethyl, C₁-6dialkylamino, e.g. dimethylamino or diethylamino, nitro, cyano, hydroxyl (-OH), formyl [HC(O)-], -CO₂H, -CO₂Alk²[where Alk² is as defined

- above], C₁-6 alkanoyl e.g. acetyl, thiol (-SH), thioC₁-alkyl, e.g. thiomethyl or thioethyl, sulphonyl (-SO₃H), C₁-6alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl (-SO₂NH₂), C₁-6alkylaminosulphonyl, e.g. methylamino-sulphonyl or ethylaminosulphonyl, C₁-6dialkylaminosulphonyl, e.g. 5 dimethylaminosulphonyl or diethylaminosulphonyl, arylaminosulphonyl, e.g. optionally substituted phenylaminosulphonyl, aralkylaminosulphonyl, e.g. optionally substituted benzylaminosulphonyl, carboxamido (-CONH₂), C₁-6alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C₁-6dialkylaminocarbonyl, e.g. dimethyl-aminocarbonyl or diethylamino-carbonyl, sulphonylamino (-NHSO₂H), C₁-6alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonyl-amino, C₁-6dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethyl-sulphonylamino, aminosulphonyl-amino (-NHSO₂NH₂), C₁-6alkylaminosulphonylamino, e.g. methylamino-sulphonylamino or ethylaminosulphonylamino, C₁-6dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, 10 C₁-6alkanoylamino, e.g. acetylarnino, C₁-6alkanoylamino C₁-6alkyl, e.g. acetylaminomethyl or C₁-6alkoxycarbonylamino, e.g. methoxycarbonyl-amino, ethoxycarbonylamino or t-butoxycarbonylamino groups.
- 15 20 Where desired, two R¹⁰ substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C₂-6alkylenedioxy group such as ethylenedioxy.

It will be appreciated that where two or more R¹⁰ substituents are present, 25 these need not necessarily be the same atoms and/or groups. The R¹⁰ substituents may be present at any ring carbon atom away from that attached to the rest of the molecule of formula (1). Thus, for example, in phenyl groups represented by R⁵ any substituent may be present at the 2-, 3-, 4-, 5- or 6- positions relative to the ring carbon atom attached to the 30 remainder of the molecule.

In the compounds of formula (1), when an ester group is present, for example a group -CO₂Alk² this may advantageously be a metabolically labile ester.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

5 Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isethionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

10 15 Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

20 Particular useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

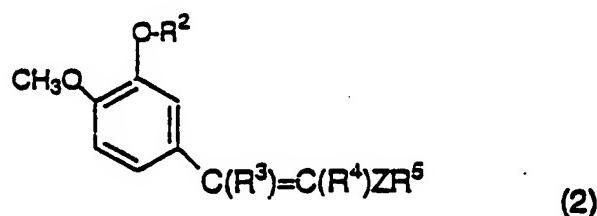
25 Prodrugs of compounds of formula (1) include those compounds for example esters, alcohols or amines, which are convertible, *in vivo*, by metabolic means, e.g. by hydrolysis, reduction, oxidation or transesterification, to compounds of formula (1).

30 In general in compounds of formula (1), the group R⁵ and the phenyl ring to which the group C(R³)=C(R⁴)ZR⁵ is attached are in a "trans" position relative to one another.

35 In the compounds of formula (1), the group Y is preferably an -OR¹ group, especially where R¹ is an optionally substituted C₁₋₃alkyl group, particularly an ethyl group or, especially, a methyl group. Especially useful substituents which may be present on R¹ groups include one, two or three fluorine or chlorine atoms.

The group X in compounds of formula (1) is preferably -O-.

5 A particularly useful group of compounds of formula (1) has the formula
 (2):



10 where R² is an optionally substituted cycloalkyl group; R³, R⁴, R⁵ and Z are as defined for formula (1); and the salts, solvates, hydrates and N-oxides thereof.

In the compounds of formulae (1) and (2) R² is preferably an optionally substituted cyclopentyl group. In particular, R² is a cyclopentyl group.

15 The group R³ in compounds of formulae (1) or (2) is preferably a -CH₃ group, or especially a hydrogen atom.

20 In compounds of formulae (1) or (2) the group R⁴ is preferably a hydrogen atom, a -CN or a -CH₃ group.

Z in the compounds of formulae (1) or (2) is preferably -(CH₂)_n- where n is zero, 1 or 2. In particular, however, Z is especially -(CH₂)_n- where n is zero.

25 R⁵ in the compounds of formulae (1) or (2) is preferably an optionally substituted phenyl group, particularly a phenyl group optionally substituted by one, two or more R¹⁰ groups, and is especially a 2-, 3- or 4-monosubstituted or 2,6-disubstituted phenyl group. Particular substituents 30 include halogen atoms, especially fluorine or chlorine atoms and nitro, amino, alkoxy, haloalkyl, hydroxy, -NHCOR^{7a}, -NHCONHR^{7a} and -NHSO₂R^{7a} groups.

Particular R⁵ groups include 2-nitrophenyl, 2-haloalkylphenyl, e.g. 2-trifluoroalkylphenyl, 2-halophenyl, e.g. 2-fluorophenyl, 2-chlorophenyl, or 2-bromophenyl, 3-halophenyl, e.g. 3-fluorophenyl, 4-hydroxyphenyl, 2,6-di-halophenyl, e.g. 2,6-difluorophenyl, or 2,6-dichlorophenyl and 2,6-dialkoxyphenyl, e.g. 2, 6-dimethoxyphenyl.

Other particularly useful R⁵ groups in compounds of formulae (1) and (2) include 2-,3- and 4-pyridinyl, thienyl e.g. 2-thienyl, pyridazinyl, e.g. 3- or 4-pyridazinyl, and imidazolyl e.g. 1-, 2-, 4- or 5-imidazolyl groups, optionally substituted by one, two or more R¹⁰ groups, especially halogen atoms, e.g. fluorine or chlorine atoms, e.g. 3,5-dichloro-4-pyridinyl, nitro, amino, alkoxy, haloalkyl, hydroxy, -NHCOR^{7a}, -NHCONHR^{7a} or -NHSO₂R^{7a} groups.

Particularly useful groups of compounds of formulae (1) or (2) are those wherein R³ is a hydrogen atom, R⁴ is a hyarogen atom, or a -CH₃ or -CN group and Z is a group (CH₂)_n where n is zero, and the salts, solvents, hydrates and N-oxides thereof. Especially useful compounds in groups of these types are those wherein R⁵ is an optionally substituted phenyl or pyridinyl group.

Particularly useful compounds according to the invention are

- 25 (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-hydroxyphenyl)propanenitrile;
- (E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridine;
- (Z)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridine;
- (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-nitrophenyl)propanenitrile;
- 30 (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4,5-dichloro-1-imidazolyl)propanenitrile
- (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)propanenitrile;
- (E)-4-[2-[1-(3-Cyclopentyloxy-4-methoxy)phenyl]-1-propenyl]pyridine;
- (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-thienyl) propanenitrile;
- 35 (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2,6-difluorophenyl)propanenitrile;

- (E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]-3,5-dichloropyridine; (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2,6-dichlorophenyl)-propanenitrile; N-(4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]-3-pyridyl)phenylsulphonamide; (E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]-3-nitropyridine; (E)-2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridine; (E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyrimidine; or (E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridazine; and the salts, solvates, hydrates and N-oxides thereof.

Compounds according to the invention are selective and potent orally active inhibitors of PDE IV. The ability of the compounds to act in this way may be simply determined by the tests described in the Examples 15 hereinafter.

The compounds according to the invention are thus of particular use in the prophylaxis and treatment of human or animal diseases where an unwanted inflammatory response or muscular spasm (for example bladder 20 or alimentary smooth muscle spasm) is present and where the elevation of cAMP levels may be expected to prevent or alleviate the inflammation and relax muscle.

Particular uses to which the compounds of the invention may be put 25 include the prophylaxis and treatment of asthma, especially inflamed lung associated with asthma, cystic fibrosis, or in the treatment of inflammatory airway disease, chronic bronchitis, eosinophilic granuloma, psoriasis and other benign and malignant proliferative skin diseases, endotoxic shock, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the 30 myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis and atherosclerosis.

35 Compounds of the invention also suppress neurogenic inflammation through elevation of cAMP in sensory neurones. They are, therefore,

analgesic, anti-tussive and anti-hyperalgesic in inflammatory diseases associated with irritation and pain.

Compounds according to the invention may also elevate cAMP in 5 lymphocytes and thereby suppress unwanted lymphocyte activation in immune-based diseases such as rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease.

Compounds according to the invention have also been found to reduce 10 gastric acid secretion and therefore can be used to treat conditions associated with hypersecretion.

Compounds of the invention suppress cytokine synthesis by inflammatory 15 cells in response to immune or infectious stimulation. They are, therefore, useful in the treatment of bacterial, fungal or viral induced sepsis and septic shock in which cytokines such as tumour necrosis factor (TNF) are key mediators. Also compounds of the invention suppress inflammation and pyrexia due to cytokines and are, therefore, useful in the treatment of 20 inflammation and cytokine-mediated chronic tissue degeneration which occurs in diseases such as rheumatoid or osteo-arthritis.

Over-production of cytokines such as TNF in bacterial, fungal or viral 25 infections or in diseases such as cancer, leads to cachexia and muscle wasting. Compounds of the invention ameliorate these symptoms with a consequent enhancement of quality of life.

Compounds of the invention also elevate cAMP in certain areas of the brain and thereby counteract depression and memory impairment.

Compounds of the invention suppress cell proliferation in certain tumour 30 cells and can be used, therefore, to prevent tumour growth and invasion of normal tissues

For the prophylaxis or treatment of disease the compounds according to 35 the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical

composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form
5 suitable for oral, buccal, parenteral or nasal administration, or a form suitable for administration by inhalation or insufflation. Forms suitable for oral administration are particularly useful.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution
10 with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.
15

Preparations for oral administration may be suitably formulated for adult or pediatric use and/or to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or
30 lozenges formulated in conventional manner.

The compounds of formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form. The compositions for injection may take such forms as suspensions, solutions
35 or emulsions in oily or aqueous vehicles, and may contain formulatory

agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

5 In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection. For transdermal administration, the compounds according to the invention may be formulated in delivery vehicles such as patches,

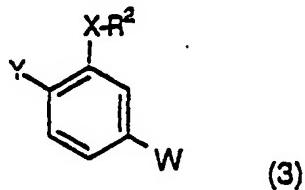
10 For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

15 The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispense device may be accompanied by instructions for administration.

20 The quantity of a compound of the invention required for the prophylaxis or treatment of a particular inflammatory condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg, e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration, and around 0.05mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

25 The compounds according to the invention may be prepared by the following processes. The symbols Y, R², R³, R⁴, R⁵, X and Z, when used in the formulae below are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated.

Thus according to a further aspect of the invention, a compound of formula (1) may be prepared by reacting a compound of formula (3):



5

where

- (a) W is a $-C(O)R^3$ group wherein R^3 is as defined for formula (1) but is not a $-CN$ or $-CH_2CN$ group, with a compound $R^5ZCH_2R^4$; or where
 - (b) W is a $-CH_2R^3$ group with an aldehyde or ketone R^5ZCOR^4 , where R^4 is as just defined for R^3 ; or where
 - (c) W is a $-CO(R)^3$ group with a silane derivative $Alk_3SiCH(R^4)(R^5)$, where Alk is an alkyl group; in the presence of a base or an acid in a suitable solvent.
- 15 Bases for use in these reactions include inorganic bases, for example alkali and alkaline earth metal bases, e.g. hydroxides, such as sodium or potassium hydroxide; alkoxides, for example sodium ethoxide, and organic bases, for example amines such as piperidine; or an organolithium, such as an alkyllithium, e.g. n-butyllithium. Suitable solvents include alcohols such as ethanoi, or ethers such as tetrahydrofuran. Acids for use in the reaction include organic acids, e.g. carboxylic acids such as acetic acid.
- 20

The reaction may be performed at any suitable temperature, for example from around $-78^\circ C$ to ambient temperature to the reflux temperature depending on the nature of the starting materials.

25

In general, the base, acid, solvent and reaction conditions may be selected depending on the nature or the starting materials, from a range of known alternatives for reactions of this type.

30

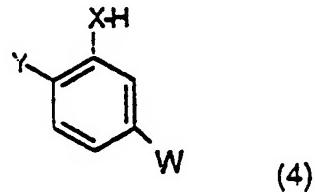
In silane derivatives of formula $Alk_3SiCH(R^4)(R^5)$, Alk may be for example a C_{1-6} alkyl group such as a methyl group. Derivatives of this type may be prepared for example by reacting a compound $R^5-CH_2-R^4$ with a silane

derivative, such as chlorotrimethylsilane, in the presence of a base, e.g. lithium diisopropylamide, in a solvent, e.g. tetrahydrofuran, at a low temperature e.g. around -10°C.

- 5 The starting materials $R^5ZCH_2R^4$, R^5ZCOR^4 , and $R^5CH_2R^4$ are either known compounds or may be prepared from known starting materials by methods analogous to those used for the preparation of the known compounds.
- 10 Intermediates of formula (3) where W is a $-C(O)R^3$ group where R^3 is an alkyl group, such as a methyl group, may be prepared by reacting an aldehyde of formula (3) where W is a $-CHO$ group with an organometallic reagent, such as methylmagnesiumbromide, in a solvent, e.g. tetrahydrofuran, at low temperature, e.g. around 10°C, followed by 15 oxidation with an oxidising agent, such as manganese dioxide, in a solvent, e.g. dichloromethane.

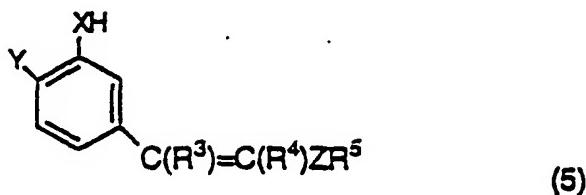
Alternatively, intermediates of formula (3) may be prepared by alkylation of a corresponding compound of formula (4)

20



- using a compound R^2Hal [where Hal is a halogen atom such as a bromine or chlorine atom] where necessary in the presence of a base such as caesium or potassium carbonate or an alkoxide such as potassium t-butoxide, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide at ambient temperature or above e.g. around 40°C to 50°C.
- 30 Intermediates of formula (4) are either known compounds or may be prepared from known starting materials by methods analogous to those used for the preparation of the known compounds.

In another aspect of the invention, a compound of formula (1) may be prepared by alkylation of a compound of formula (5)



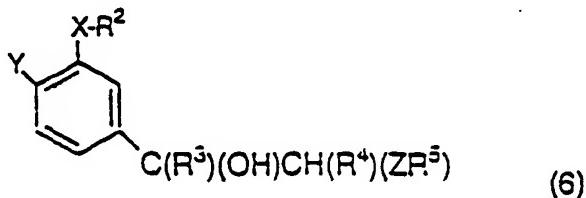
5

with a halide R^2Hal , or with an alcohol R^2OH .

The alkylation with the halide R^2Hal may be performed using the reagents and conditions described above for the preparation of compounds of formula (4). Alkylation using an alcohol R^2OH may be performed in the presence of a phosphine, such as triphenylphosphine, and an activator, for example diethyl azodicarboxylate, in the presence of an organic base such as triethylamine in a solvent such as tetrahydrofuran at an elevated temperature, e.g. the reflux temperature [see for example Mitsunobu, O., *Synthesis*, 1981, 1].

Intermediates of formula (5) may be prepared by reaction of an aldehyde or ketone of formula (4) with a compound $\text{R}^5\text{ZCH}_2\text{R}^4$ as described above for the preparation of compounds of formula (1) from compounds of formula (3). In this reaction the group X-H may need to be in a protected state. Conventional hydroxy, amino or thiol protecting groups may be used in accordance with standard practice [see, for example, Green T.W., in "Protective Groups in Organic Synthesis" John Wiley and Sons, 1981].

25 According to a further aspect of the invention a compound of formula (1) may be prepared by dehydration of an alcohol of formula (6)



using an acid at an elevated temperature.

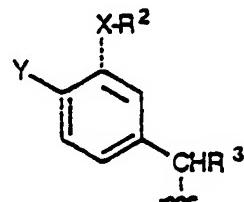
Suitable acids include for example phosphoric or sulphonic acids, e.g. 4-toluenesulphonic acid. The reaction may be performed in an inert organic

5 solvent, for example a hydrocarbon such as toluene, at an elevated temperature, for example the reflux temperature.

Intermediate alcohols of formula (6) may be prepared by reaction of a ketone of formula (3) with an organometallic reagent R^4R^5ZCHM [where M is a metal atom, for example a lithium atom] in a solvent such as an ether, e.g. a cyclic ether such as tetrahydrofuran, at a low temperature e.g. around -70°C to ambient temperature.

Reagents R^4R^5ZCHM are either known compounds or may be prepared, 15 preferably in situ during the above process, by reaction of a compound $AlkCH_2M$ or $[Alk]_2NM$ [where Alk is an alkyl group such as a n-propyl or i-propyl group] with a compound $R^4R^5ZCH_2$ using the just mentioned reaction conditions.

20 According to a still further aspect of the invention, a compound of formula (1) may be prepared by reaction of a phosphonium salt $R^{13}P^+Ar_3Hal^-$ where R^{13} is a group of formula



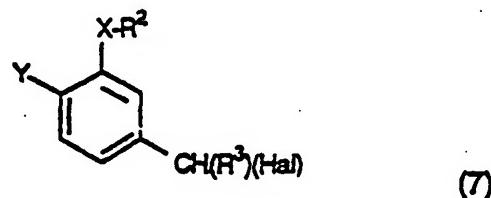
25

Ar is an aryl group such as a phenyl group and Hal is a halogen atom such as a chlorine, bromine or iodine atom, with a compound R^5ZCOR^4 in the presence of a base in a suitable solvent.

30 Bases for use in this reaction include alkoxides, for example alkali metal alkoxides such as sodium ethoxide or organometallic bases such as phenyllithium. Suitable solvents include alcohols, such as ethanol, and

ethers, e.g. cyclic ethers such as tetrahydrofuran. The reaction may generally be performed at ambient temperature.

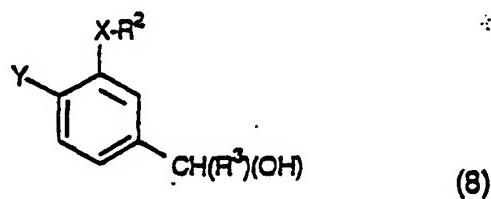
5 Intermediate phosphonium salts of formula $R^{13}P^+Ar_3Hal^-$ may be prepared by reaction of a halide of formula (7)



with a phosphine Ar_3P .

10

Intermediate halides of formula (7) may be prepared by reaction of an alcohol of formula (8)

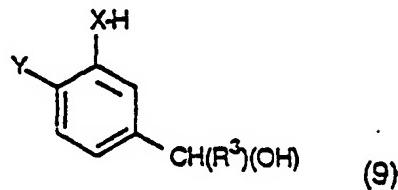


15

with a hydrogen halide in a solvent such as an ether.

Intermediate alcohols of formula (8) may be prepared by alkylation of a compound of formula (9)

20

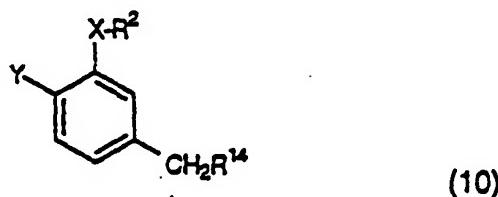


with a halide R^2Hal as described above for the preparation of compounds of formula (1) from intermediates of formula (5).

25

Intermediates of formula (9) are either known compounds or may be prepared by methods analogous to those used for the preparation of the known compounds.

- 5 In yet another aspect of the invention, a compound of formula (1) may be prepared by reaction of a phosphonate ester of formula (10)



- 10 [wherein R¹⁴ is a -P(O)(OR¹⁵)(OR¹⁶) group, where R¹⁵ and R¹⁶, which may be the same or different is each an alkyl, e.g. ethyl, aryl, e.g. phenyl or aralkyl e.g. benzyl group] with a compound R⁵ZCOR⁴ in the presence of a base in a suitable solvent.
- 15 Suitable bases include hydrides such as sodium hydride and alkoxides, for example alkali metal alkoxides such as sodium ethoxide. Solvents include others, for example cyclic ethers such as tetrahydrofuran.

Phosphonate esters of formula (10) may be prepared by a Michaelis 20 Arbuzov reaction of a halide of formula (8) with a phosphite P(OR¹⁵)₂OR¹⁶.

- Compounds of formula (1) may also be prepared by interconversion of other compounds of formula (1). Thus, for example, a substituted 25 monocyclic or bicyclic aryl group R⁵ in compounds of formula (1) may generally be obtained by an appropriate substitution reaction using the corresponding unsubstituted compound of formula (1) and a R¹⁰ containing nucleophile or electrophile. Similarly, where it is desired to obtain a compound of formula (1) where R³ and/or R⁴ is other than a 30 hydrogen atom, an appropriate nucleophile and reagents and/or reaction conditions favouring nucleophilic addition, may be used with the corresponding compound of formula (1) where R³ and R⁴ is a hydrogen atom. Alternatively, a group R³ and/or R⁴ in formula (1) may be

manipulated using conventional chemical procedures to yield other groups R³ and/or R⁴.

- 5 Thus, in one example of an interconversion process a compound of formula (1) wherein R⁵ contains a -CH₂NH₂ substituent may be prepared by reduction of a corresponding compound wherein R⁵ contains a nitrile group, using for example a complex metal hydride such as lithium aluminium hydride in a solvent such as an ether e.g. diethylether.
- 10 In a further example, a compound of formula (1) wherein R⁵ contains -NHCOR^{7a}, -NHCONHR^{7a}, -NHCON(R^{7a})₂, -NHCSR^{7a} or alkanoylamino-alkyl substituent may be prepared by acylation or thiolation of a corresponding compound wherein R⁵ contains a -NH₂ or alkylamino group
- 15 by reaction with an acyl halide e.g. an acyl chloride, an acyl alkyl or aryl isocyanate or a thiol halide in the presence of a base, such as a tertiary amine e.g. triethylamine or pyridine, optionally in a solvent such as dichloromethane.
- 20 In a still further example, a compound of formula (1) wherein R⁵ contains an alkoxy substituent may be prepared by alkylation of a corresponding compound wherein R⁵ contains a hydroxyl group by reaction with a compound AlkHal [where Alk is a C₁₋₆ alkyl group such as a methyl or ethyl group and Hal is a halogen atom such as an iodine atom] in the
- 25 presence of a base such as caesium or potassium carbonate in a dipolar aprotic solvent such as an amide, e.g. dimethylformamide at ambient temperature or above.
- 30 In another example, a compound of formula (1) wherein R³ and/or R⁴ is a -CN or -CH₂CN group may be prepared by dehydration of a corresponding amide where R³ and/or R⁴ is -CONH₂ or -CH₂CONH₂ using for example trifluoroacetic anhydride in the presence of a base such as pyridine in a solvent such as tetrahydrofuran.
- 35 N-oxides of compounds of formula (1) may be prepared by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen

peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C.

- 5 Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate acid or base in a suitable solvent using conventional procedures.

The following examples illustrate the invention.

- 10 The following abbreviations are used:

DMF	dimethylformamide
THF	tetrahydrofuran
DME	dimethoxyethane
15 EtOAc	ethyl acetate
Et ₂ O	diethylether
RT	room temperature
LDA	lithium diisopropylamide

20 **INTERMEDIATE 1**

a) **3-Cyclopentyloxy-4-methoxybenzaldehyde**

Caesium carbonate (214g, 0.66mol) was added to a mixture of 3-hydroxy-4-methoxybenzaldehyde (100g, 0.66mol) and cyclopentyl bromide (98g, 0.66mol) in anhydrous DMF (50ml). The reaction mixture was stirred at 25 RT for 16h then treated with a further portion of cyclopentyl bromide (98g, 0.66mol) and caesium carbonate (214g, 0.66mol). After a further 6h at RT, the mixture was filtered and concentrated in vacuo. The residue was dissolved in dichloromethane (300ml) and washed with sodium hydroxide solution (10%; 2x150ml). The organic layer was dried ($MgSO_4$), 30 concentrated in vacuo, and distilled (150°C, 10⁻²mbar) to afford the title compound (130g) as a viscous colourless oil. (Found: C, 70.38; H, 7.48. $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32%); δ_H ($CDCl_3$) 1.5-2.0 (8H, br m, CH_2), 3.87 (3H, s, OMe), 4.80 (1H, br m, OCH_2CH_2), 6.90 (1H, d, \downarrow 3.7Hz, ArH ortho to OMe), 7.30-7.45 (2H, m, 2xArH meta to OMe), and 35 9.77 (1H, s, ArCHO).

b) 3-Cyclopentyloxy-4-methoxybenzylalcohol

From 3-hydroxy-4-methoxybenzyl alcohol (50g, 0.324mol), cyclopentyloxybromide (70ml, 0.648mol), caesium carbonate (72.83g, 0.222mol) and sodium iodide (5.63g, 0.037mol). Chromatography (SiO₂; EtOAc-C₆H₁₄ 5 1:3) to yield the title compound (25.782g). (Found C, 69.92; H, 8.18. C₁₃H₁₈O₃ requires C, 70.25; H, 8.16).

INTERMEDIATE 2

3,5-Dichloro-4-methylpyridine

10 3,5-Dichloropyridine (2.04g, 13.5mmol) in THF (5ml) was added dropwise to a solution of LDA [prepared from diisopropylamine (1.9ml, 13.5mmol) and n-butyllithium (1.6M, 8.4ml, 13.5mmol)] in THF (25ml) at -70°C. After stirring at this temperature for 5 min, iodomethane (0.85ml, 13.5 mmol) was added and the reaction mixture stirred for a further 1.5h at -70°C.

15 Saturated sodium hydrogen carbonate solution (20ml) and dichloromethane (20ml) was added and the organic phase separated, dried (MgSO₄), and concentrated in vacuo. The residue was subjected to chromatography (SiO₂; Et₂O-hexane, 1:3) to afford the title compound (1.16g) as a pale yellow solid; δH (CDCl₃) 2.46 (3H, s, Me), and 8.36 (2H, 20 s, pyridine H₂, H₆).

INTERMEDIATE 3

a) 4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxyethyl]-3,5-dichloropyridine

25 Intermediate 2 (2.22g, 13 mmol) in THF (40ml) was added dropwise to a solution of LDA [prepared from diisopropylamine (2.4ml, 17mmol) and n-butyllithium (1.6M, 10.2ml, 16mmol)] in THF (50ml) at -70°C and the mixture stirred at this temperature for 0.25h. A solution of Intermediate 1 (3.32g, 15mmol) in THF (50ml) was then added at -70°C and the reaction mixture allowed to warm to RT overnight. Saturated ammonium chloride solution (50 ml) and dichloromethane (50ml) was added and the organic phase separated, dried (MgSO₄), and concentrated in vacuo. The residual yellow solid was triturated with hot Et₂O to afford the title compound (2.65g) as a white solid m.p. 139-140°C (Found: C, 59.49; H, 5.68; N, 3.57. C₁₉H₂₁Cl₂NO₃ requires C, 59.69; H, 5.53; N, 3.66%); δH (CDCl₃) 1.5-2.1 (9H, br m, CH₂)₄ + OH), 3.2-3.5 (2H, m, CH₂Ar), 3.81 (3H,

s, OMe), 4.7 (1H, br m, OCH₂CH₂), 5.01 (1H, dd, J 5.8, 8.4Hz, CHOH), 6.75-6.9 (3H, m, ArH ortho to OMe + 2xArH meta to OMe), and 8.36 (2H, s, pyridine H₂, H₆); m/z 383 (10%), 381 (17), 221 (46), 163 (49), 161 (74), 153 (100), 152 (24), 151 (17), 125 (27), 93 (48), 65 (25), and 41 (34).

5

The following intermediates were prepared in a manner similar to Intermediate 3a:

10 b) 2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-hydroxyethyl]pyridine

From 2-methylpyridine (1.02g, 11mmol), LDA (1.0 equiv), and Intermediate 1 (2.45g, 11mmol). The crude product was subjected to chromatography (SiO₂; Et₂O) to afford the title compound (2.67g) as a yellow solid m.p. 94-96°C (Found: C, 72.89; H, 7.43; N, 4.58. C₁₉H₂₃NO₃ requires C, 72.82; H, 7.40; N, 4.47%); δH (CDCl₃) 1.5-2.1 (9H, br m, (CH₂)₄ + OH), 3.09 (2H, d, J 6.1 Hz, CH₂Ar), 3.80 (3H, s, OMe), 4.74 (1H, br, d, OCH₂CH₂), 5.06 (1H, t, J 6.1Hz, CHOH), 6.8-7.2 (5H, m, ArH ortho to OMe + 2xArH meta to OMe + pyridine H₃, H₄), 7.56 (1H, m, pyridine H₅), and 8.47 (1H, dm, J 4.5Hz, pyridine H₆); m/z 313 (M⁺, 5%), 153 (16), 152 (90), 151 (53), 93 (100), 80 (17), and 41 (14).

25 c) 4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxyethyl]pyrimidine

From 4-methylpyrimidine (2.15g, 23.6mmol), LDA (1.0 equiv), and Intermediate 1 (5.12g, 23.0mmol). The crude product was subjected to chromatography (SiO₂; Et₂O) to afford the title compound (3.83g) as an amber oil. (HCl salt m.p. 211-213°C) (HCl salt Found: C, 62.24; H, 6.68; N, 8.06. C₁₈H₂₃N₂O₃ requires C, 61.44; H, 6.87; N, 7.96%); δH (CDCl₃) 1.5-2.1 (8H, br m, (CH₂)₄), 3.10 (2H, d, J 6.5 Hz, CH₂Ar), 3.80 (3H, s, OMe), 4.15 (1H, br, s OH), 4.74 (1H, br, m, OCH₂CH₂), 5.10 (1H, t, J 6.5Hz, CHOH), 6.75-6.9 (3H, m, ArH ortho to OMe + 2xArH meta to OMe), 7.09 (1H, dd, J 4.9Hz, pyrimidine H₅), 8.53 (1H, d, J 4.9Hz, pyrimidine H₆), and 9.07 (1H, d, J 4.0Hz, pyrimidine H₂); m/z 314 (M⁺, 16%), 296 (19), 228 (23), 227 (75), 166 (18), 153 (22), 152 (20), 151 (16), 94 (100), and 41 (26).

d) 4-[2-(1-(3-Cyclopentyloxy-4-methoxyphenyl)-1-hydroxylpropyl]pyridine

From 4-ethylpyridine (2.50g, 2.65ml, 23.33mmol), LDA and Intermediate 1

- 5 (5.14g, 23.33mmol). Recrystallisation (CHCl₃/hexane) afforded the title compound (0.582g) as colourless fluffy needles. m.p. 131.5-132.3°C. (Found: C, 72.38; H, 7.74; N, 4.22. C₂₀H₂₅NO₂·1/4H₂O requires C, 72.44; H, 7.56; N, 4.10%).

10

INTERMEDIATE 4

a) 4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxyethyl]pyridazine

- 15 η -Butyllithium (1.6M in hexanes) (9.5ml, 6.0mmol) was added dropwise to a solution of methylpyridazine (0.47g, 5.0mmol) in THF (25ml) at -70°C. The reaction mixture was allowed to stir at this temperature for 0.5h then a solution of Intermediate 1 (1.1g, 5.0mmol) in THF (20ml) was added. The mixture was allowed to warm to RT then partitioned between dichloromethane (25ml) and saturated sodium hydrogen carbonate solution (25ml). The organic phase was separated, dried (MgSO₄), and concentrated in vacuo to afford the title compound which was used in the next step [Example 7a] without any further purification.

- 20 The following Intermediates were prepared in a manner similar to Intermediate 4 a.

b) 4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxyethyl]pyridine

- 25 From 4-methylpyridine (3.00g, 32.1mmol), η -butyllithium (32.1mmol), and Intermediate 1 (6.82g, 31.0mmol). The crude product was subject to chromatography [SiO₂; EtOAc-hexane, 3:2 (500ml) to 4:1 (1000ml) then EtOAc-methanol 9:1 (1500ml)] to afford the title compound (9.68g) as fine white needles m.p. 97-101°C (from toluene) δ H (CDCl₃) 1.5-2.0 (8H, br m, (CH₂)₄, 2.45(1H, br, s, CHO_H), 2.96 (2H, d, \downarrow 6.5 Hz, CH₂ pyridine), 3.80 (3H, s, OMe), 4.70 (1H, br, m, OCH₂CH₂), 4.81 (1H, t, \downarrow 6.5Hz, CH₂OH),

6.76(3H, s, ArH ortho to OMe + 2xArH meta to OMe), 7.00 (2H, dm, \downarrow 4.5Hz, pyridine H₃, H₅), and 8.33 (2H, dm, \downarrow 4.5Hz, pyridine H₂, H₆).

c) 2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-hydroxyethyl]pyrazine

From methylpyrazine (0.94g, 11mmol), n-butyllithium (1.6M; 6.9ml, 11mmol), and Intermediate 1 (2.2g, 10mmol) to afford the title compound which was used in the next step [Example 7c)] without any further purification.

10

INTERMEDIATE 5

(3-Cyclopentyloxy-4-methoxyphenyl)-3-hydroxy-2-(phenylmethyl)propane-1-nitrile

15 3-Phenylpropionitrile (2.62g, 20mmol) was added dropwise to a solution of LDA [prepared from n-BuLi (1.6M solution in hexanes) (14ml, 22mmol) and N,N-diisopropylamine (3.5ml, 25mmol)] in THF (100ml) at -70°C. A solution of Intermediate 1 (4.4g) in THF (25ml) was then added and the reaction mixture was allowed to warm to RT then poured into NaHCO₃ solution (50ml) and extracted with CH₂Cl₂ (2x50ml). The extract was dried (Na₂SO₄), concentrated in vacuo, and the residue subjected to chromatography (SiO₂; Et₂O-hexane, 1:1) to afford the title compound (4.34g) as a pale yellow oil; m/z 351 (M⁺, 10%), 221 (22), 153 (100), 152 (19), 151 (15), 125 (15), 93 (25), 92 (25), 65 (14) and 41 (16).

20

INTERMEDIATE 6

(3-Cyclopentyloxy-4-methoxyphenyl)methyl ketone

30 To a solution of methylmagnesiumbromide (5.44ml) in THF (150ml) at 10°C was added Intermediate 1. The reaction mixture was left to stir at RT for 5-6hr, then NH₄Cl and Et₂O (100ml) were added and the solution stirred for another 90 min (the solution went from hazy to clear). The layers were separated, the aqueous layer was extracted with Et₂O (50ml) 35 the combined organic layer was extracted with a saturated bicarbonate solution (100ml) then brine (100ml). Evaporation in vacuo afforded 1-

methoxy-2-cyclopentyloxy-4-(1-hydroxyethyl)benzene which was dissolved in dichloromethane (300ml) before adding MnO₂ (10eq). The reaction mixture was stirred for 120h, then the MnO₂ was filtered off and the solvent evaporation *in vacuo*. Purification by column chromatography (SiO₂; dichloromethane-hexane, 350-150 to dichloromethane) afforded the title compound.

INTERMEDIATE 7

4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-methyl-2-hydroxyethyl]pyridine

To a cold (-78°C) solution of 4-picoline (0.80ml) in THF was added n-BuLi (5.6ml), the solution stirred for 30min then transferred to a cold suspension of cerium chloride anhydrous (2.0g) at -78°C. The reaction mixture was stirred for 1h before adding Intermediate 6 in THF then left to warm to RT overnight. 10% NH₄Cl solution and EtOAc were added, the solution was filtered through Celite, washed with EtOAC (150ml) and the organic layer was separated, washed with brine (100ml) then dried (Na₂SO₄). The solvents were evaporated *in vacuo* to afford the title compound (2.367g) as pale off-white crystals m.p. 99-101°C. Found C, 73.21; H, 7.63; N, 4.20. C₂₀H₂₅NO₃ requires C 73.37; H, 7.70; N, 4.28%. m/z (EI) 327 (M⁺, 3%), 235 (18), 166 (38), 151 (100), and 93 (54).

INTERMEDIATE 8

3-Cyclopentyloxy-4-methoxybenzyl alcohol

Intermediate 1b (0.6g, 2.7mmol) was dissolved in ethereal HCl, the solution stirred at RT and followed by thin layer chromatography until complete disappearance of the starting material. The solution was washed with saturated sodium bicarbonate solution. The organic layer extracted and dried (Na₂SO₄). Concentration *in vacuo* afforded the title compound (0.395g).

INTERMEDIATE 9

3-Cyclopentyloxy-4-methoxybenzyltriphenylphosphonium chloride

A mixture of Intermediate 8 (10.4g, 43.2mmol) and triphenylphosphine (11.5g, 43.8mmol) in toluene (100ml) was heated to reflux for 18h. The

reaction mixture was concentrated *in vacuo* and the residue triturated with acetone (250ml) to afford the title compound (19.5g) as a white solid.

INTERMEDIATE 10

5 Dielthyl 3-Cyclopentyloxy-4-methoxybenzylphosphonate

A mixture of Intermediate 8 (52.7g, 0.22mol) and sodium iodide (32.9g, 0.22mol) in triethyl phosphite (76.4g, 0.46mol) was heated at 100°C for 24h. The reaction mixture was partitioned between EtOAc (200ml) and water (200ml) and the organic layer was separated. The extract was washed (brine; 50ml), dried (MgSO_4), and concentrated *in vacuo* to give a pale yellow oil (70g). A portion (40g) of the oil was distilled (190-210°C, 10^{-2} mbar) to afford the title compound (20.3g, 27%) as a colourless oil.

15 EXAMPLE 1

a) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-thienyl)propanenitrile

2-Thiopheneacetonitrile (1.1ml, 10mmol) and Intermediate 1 (2.29g, 10mmol) was dissolved in ethanol (10ml) and added to a solution of sodium hydroxide (0.51g, 12.8mmol) in water (5ml). The reaction mixture was allowed to stir at RT for 2h then partitioned between dichloromethane (20ml) and saturated sodium hydrogen carbonate solution (15ml). The organic layer was separated, dried (MgSO_4), and concentrated *in vacuo* to give a yellow gum which was recrystallised from ethanol to afford the title compound (3.35g) as yellow crystals m.p. 100-101°C. (Found: C, 69.47; H, 5.80; N, 4.18. $\text{C}_{19}\text{H}_{19}\text{NO}_2\text{S}$ requires C, 70.13; H, 5.80; N, 4.18%); δH (CDCl_3) 1.5-2.1 (8H, br m, $(\text{CH}_2)_4$), 3.87 (3H, s, OMe), 4.85 (1H, br m, OCHCH_2), 6.83 (1H, d, \downarrow 8.5Hz, ArH ortho to OMe), 7.00 (1H, dd, \downarrow 4.5, 3.5Hz, thiophene H₄), 7.15-7.3 (4H, m, ArH para to cyclopentyloxy + $\text{CH}=\text{CCN+thiophene H}_3$, H₅), and 7.60 (1H, d, \downarrow 2.2Hz, ArH ortho to cyclopentyloxy); m/z 326 ($M^+ \div 1$, 23%), 325 (M^+ , 87), 259 (34), 258 (85), 257 (100), 224 (24), 214 (27), 197 (21), 196 (93) and 41 (29).

35 The following compounds were prepared in a manner similar to the compound of Example 1 a.

b) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenyl-propenenitrile

From phenylacetonitrile (0.52g, 4.4mmol) and Intermediate 1 (0.95g, 4.3mmol). Chromatography (SiO₂; EtOAc-hexane) gave the title compound (0.81g) as a yellow solid m.p. 84-86% (Found: C, 78.83; H, 6.60; N, 4.38. C₂₁H₂₁NO₂ requires C, 78.97; H, 6.63; N, 4.39%); δH (CDCl₃) 1.5-2.1 (8H, m, (CH₂)₄), 3.86 (3H, s, OMe), 4.82 (1H, br m, OCH₂CH₂), 6.85 (1H, d, J 8.8Hz, ArH ortho to OMe), 7.15-7.7 (7H, m, ArH para to cyclopentyloxy + CH=CCN + C₆H₅), and 7.67 (1H, d, J 2.3Hz, ArH ortho to cyclopentyloxy); m/z 319 (M⁺, 33%), 252 (49), 251 (100), 218 (15), 208 (32), 190 (48), 180 (15), 152 (15) and 41 (20).

c) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-pyridyl)-propenenitrile

From 2-pyridylacetonitrile (11mmol) and Intermediate 1 (2.20g, 10mmol). Trituration of the crude product with ethanol gave the title compound (2.40g) as a yellow solid m.p. 82.5-83°C (Found: C, 74.87; H, 6.27; N, 8.46. C₂₀H₂₀N₂O₂ requires C, 74.98; H, 6.29; N, 8.74%); δH (CDCl₃) 1.5-2.1 (8H, br m, (CH₂)₄), 3.824 (3H, s, OMe), 4.80 (1H, br m, OCH₂CH₂), 6.84 (1H, d, J 8.6Hz, ArH ortho to OMe), 7.05-7.25 (1H, m, pyridine H₅), (1H, dd, J 8.6, 1.95Hz, ArH para to OMe), 7.6-7.75 (3H, m ArH ortho to cyclopentyloxy+ pyridine H₃H₄), 8.29 (1H, s, CH=CCN) and 8.52 (1H, ca.o. J 4.6 Hz, pyridine H₆); m/z 320 (M⁺, 15%), 252 (38), 251 (100), 237 (5), 236 (10), 209 (5), 179 (5), and 41 (8).

d) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(3-pyridyl)-propenenitrile

From 3-pyridylacetonitrile (2.35ml, 22mmol) and Intermediate 1 (4.40g, 20mmol). Chromatography (SiO₂; EtOAc) gave the title compound (5.31g) as a pale yellow solid m.p. 86.5-87.5°C (Found: C, 74.80; H, 6.26; N, 8.74. C₂₀H₂₀N₂O₂ requires C, 74.98; H, 6.29; N, 8.74%); δH (CDCl₃) 1.5-2.1 (8H, br m, (CH₂)₄), 3.87 (3H, s, OMe), 4.82 (1H, br m, OCH₂CH₂), 6.86 (1H, d, J 8.6Hz, ArH ortho to OMe), 7.2-7.4 (2H, m, ArH para to OMe +

pyridine H₃), 7.42 (1H, s, CH=CCN), 7.70 (1H, d, J 2.0Hz, ArH ortho to cyclopentyloxy), 7.87 (1H, dm, J 7.6Hz, pyridine H₄), 8.53 (1H, dd, J 4.8, 1.3Hz, pyridine H₆) and 8.84 (1H, d, J 2.4Hz, pyridine H₂); m/z 320 (M⁺, 20%), 252 (100), 251 (67), 234 (20), 223 (27), 205 (27), 151 (50), 69 (22), 5 and 41 (31).

5 e) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)-propanenitrile

From 4-pyridylacetonitrile (1.7g, 11mmol) and Intermediate 1 (2.20g, 10 20mmol). Trituration of the crude product with ethanol gave the title compound (2.75g) as an orange solid m.p. 125-127°C. (Found: C, 74.84; H, 6.29; N, 8.33. C₂₀H₂₀N₂O₂ requires C, 74.98; H, 6.29; N, 8.74%); δ_H (CDCl₃) 1.5-2.1 (8H, br m, (CH₂)₄), 3.84 (3H, s, OMe), 4.83 (1H, br m, OCH₂CH₂), 6.83 (1H, d, J 8.2Hz, ArH ortho to OMe), 7.26 (1H, dd, J 8.2, 2.2Hz, ArH para to OMe), 7.44 (2H, dd, J 4.7, 1.7Hz pyridine H₃, H₅), 7.53 (1H, s, CH=CCN) 7.69 (1H, d, J 2.2Hz, ArH ortho to cyclopentyloxy), 8.56 (2H, dd, J 4.7, 1.5 Hz, pyridine H₂, H₆); m/z 320 (M⁺, 28), 253 (19), 252 (100), 251 (59), 224 (15), 223 (38), 209 (10), and 41 (23).

20

f) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(1-naphthyl)-propanenitrile

From 1-naphthylacetonitrile (1.67g, 10mmol) and Intermediate 1 (2.2g, 10mmol). The reaction mixture was extracted with dichloromethane then the extract dried (MgSO₄) and concentrated in vacuo to afford the title compound (2.56g) as a yellow solid.p. 161-163°C (Found: C, 81.22; H, 6.29; N, 3.77. C₂₅H₂₃NO₂ requires C, 81.27; H, 6.27; N, 3.79%); δ_H (CDCl₃) 1.5-2.1 (8H, br m, (CH₂)₄), 3.89 (3H, s, OMe), 4.85 (1H, br m, OCH₂CH₂), 6.87 (1H, d, J 8.1Hz ArH ortho to OMe), and 7.15-8.1 (10H, m, 2xArH ortho to OMe + CH=CCN + C₁₀H₇); m/z 320 (M⁺ + 1, 30%), 369 (M⁺, 30), 302 (28), 301 (100), 268 (10), 240 (17), 202 (5), and 41 (5).

35 g) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-naphthyl)-propanenitrile

From 2-naphthylac tonitrile (1.67g, 10mmol) and Intermediate 1 (2.2g, 10mmol). The crude product was recrystallised from ethanol to afford the title compound (3.14g) as a pale yellow solid. m.p. 147-148°C (Found: C, 81.15; H, 6.24; N, 3.56. C₂₅H₂₃NO₂ requires C, 81.27; H, 6.27; N, 3.79%); δH (CDCl₃) 1.5-2.1 (8H, br m, (CH₂)₄), 3.88 (3H, s, OMe), 4.87 (1H, br m, OCH₂CH₂), 6.86 (1H, d, J 8.3Hz, ArH meta to OMe), and 7.2-8.1 (10H, m, 2xArH meta to OMe + CH=CCN + C₁₀H₇); m/z 370 (M⁺ + 1, 10%), 369 (M⁺, 40), 302 (23), 301 (100), 240 (20), 167 (12), 124 (38), and 41 (10).

10

h) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(3-thienyl)propanenitrile

From 3-thienylacetonitrile (1.2ml, 10.5mmol) and Intermediate 1 (2.21g, 10mmol). The crude product was recrystallised from ethanol to afford the title compound (2.50g) as a yellow solid m.p. 83-84°C (Found: C, 69.86; H, 5.85; N, 4.18. C₁₉H₁₉NO₂S requires C, 70.13; H, 5.89; N, 4.30%); δH (CDCl₃) 1.5-2.1 (8H, br m, (CH₂)₄), 3.86 (3H, s, OMe), 4.85 (1H, br m, OCH₂CH₂), 6.84 (1H, d, J 8.0Hz, ArH ortho to OMe) 7.15-7.5 (5H, m, para to cyclopentyloxy + CH=CCN) + thiophene H₂, H₄, H₅) and 7.62 (1H, d, J 2.2Hz, ArH ortho to cyclopentyloxy); m/z 325 (M⁺, 34%), 258 (23), 257 (100), 256 (10), 226 (11), 214 (19), 197 (12), and 196 (30).

i) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-fluorophenyl)propanenitrile

From 2-fluorophenylacetonitrile (1.35g, 10mmol) and Intermediate 1 (2.20g, 10mmol). Chromatography (SiO₂; Et₂O-hexane) gave the title compound (0.51g) as a yellow solid m.p. 70-73°C (Found: C, 74.58; H, 6.08; N, 4.03. C₂₁H₂₀NO₂ requires C, 74.76; H, 5.97; N, 4.15%); δH (CDCl₃) 1.5-2.1 (8H, br m, (CH₂)₄), 3.88 (3H, s, OMe), 4.83 (1H, br m, OCH₂CH₂), 6.85 (1H, d, J 8.6Hz, ArH ortho to OMe), 6.9-7.6 (5H, m, ArH para to cyclopentyloxy + C₆H₄F), 7.40 (1H, s, CH=CCN), and 7.69 (1H, d, J 2.2Hz, ArH ortho to cyclopentyloxy); m/z 337 (M⁺, 5%), 269 (55), 220 (13), 153 (25), 152 (100), 151 (96), 69 (17), 67 (13), and 41 (51).

35 j) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(3-fluorophenyl)propanenitrile

From 3-fluorophenylacetonitrile (1.2g, 10mmol) and Intermediate 1 (2.20g, 10mmol). The crude product was recrystallised from ethanol to afford the title compound (2.77g) as yellow crystals m.p. 114-116°C (Found: C, 74.79; H, 5.96; N, 4.07. $C_{21}H_{20}FNO_2$ requires C, 74.76; H, 5.97; N, 4.15%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br, m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.85 (1H, br m, OCH_2CH_2), 6.86 (1H, d, \downarrow 8.4Hz, ArH ortho to OMe), 7.0-7.45 (6H, m, ArH para to OMe + $CH=CCN + C_6H_4F$), and 7.68 (1H, d, \downarrow 1.8Hz, ArH ortho to cyclopentyloxy); m/z 337 (M^+ , 10%), 270 (23), 269 (100), 208 (30), 149 (13), 55 (14) and 41 (17).

10

k) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-fluorophenyl)propanenitrile

From 4-fluorophenylacetonitrile (1.3g, 10mmol) and Intermediate 1 (2.41g, 11mmol). The reaction mixture was filtered to afford the title compound (3.34g) as colourless crystals m.p. 139-141°C (Found: C, 74.80; H, 5.95; N, 4.05. $C_{21}H_{20}FNO_2$ requires C, 74.76; H, 5.97; N, 4.15%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br, m, $(CH_2)_4$), 3.87 (3H, s, OMe), 4.82 (1H, br m, OCH_2CH_2), 6.85 (1H, d, \downarrow 8.6Hz, ArH ortho to OMe), 6.95-7.2 (3H, m, ArH para to cyclopentyloxy + 2xArH ortho to F), 7.30 (1H, s, $CH=CCN$), 7.45-7.7 (3H, m, ArH ortho to OCp + 2xArH meta to F); m/z 337 (M^+ , 11%), 271 (21), 269 (100), 226 (13), 208 (25), and 41 (19).

l) (Z)-2-(3-Chlorophenyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)propanenitrile

From 3-chlorophenylacetonitrile (1.53g, 10mmol) and Intermediate 1 (2.21g, 10mmol). The crude product was recrystallised from ethanol to afford the title compound (3.01g) as yellow crystals m.p. 98-100.5°C (Found: C, 71.40; H, 5.70; N, 4.03. $C_{21}H_{20}ClNO_2$ requires C, 71.28; H, 5.70; N, 3.96%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.87 (3H, s, OMe), 4.82 (1H, br m, OCH_2CH_2), 6.85 (1H, d, \downarrow 8.4Hz, ArH ortho to OMe), and 7.2-7.7 (7H, m, 2xArH meta to OMe + $C_6H_4Cl + CH=CCN$); m/z 353 (M^+ , 26%), 288 (18), 287 (85), 286 (56), 285 (100), 224 (37), 207 (22) and 41 (45).

35 m) (Z)-2-(3-Bromophenyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)propanenitrile

From 3-bromophenyiacetonitrile (1.97g, 10mmol) and Intermediate 1 (2.24g, 10mmol). The crude product was recrystallised from ethanol to afford the title compound (2.94g) as yellow crystals m.p. 90-91.5°C (Found: C, 63.38; H, 5.01; N, 3.48. $C_{21}H_{20}BrNO_2$ requires C, 63.33 H, 5.06; N, 3.52%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.85 (1H, br m, OCH_2CH_2), 6.85 (1H, d, \perp 8.5Hz, ArH ortho to OMe), and 7.15-7.75 (7H, m, 2xArH meta to OMe + C_6H_4Br + $CH=CCN$); m/z 399 (8%), 397 (8), 332 (21), 331 (100), 330 (23), 329 (100), 235 (15), 217 (16), 207 (26), 190 (14), 178 (12), and 41 (38).

10

n) (E)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2,6-difluorophenyl) propenenitrile

From 2,6-difluorophenyiacetonitrile (1.86g, 10mmol) and Intermediate 1 (2.19g, 10mmol). Chromatography (SiO_2 ; Et_2O -hexane, 1:4) followed by

15

recrystallisation from ethanol gave the title compound (0.3g) as yellow crystals m.p. 111-113°C. (Found: C, 70.78; H, 5.37; N, 3.85. $C_{21}H_{19}F_2NO_2$ requires C, 70.97 H, 5.39; N, 3.94%); δ_H ($CDCl_3$) 1.4-1.8 (8H, br s, $(CH_2)_4$), 3.80 (3H, s, OMe), 4.22 (1H, br s, OCH_2CH_2), 6.52 (1H, br s, ArH ortho to OMe), and 6.7-7.5 (6H, m, 2xArH meta to OMe + $C_6H_4F_2$); m/z 355 (M $^+$, 21%), 288 (19), 287 (100), 244 (11), 152 (48), 151 (31), and 41 (22).

o) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2,6-dichlorophenyl) propenenitrile

25

From 2,6-dichlorophenyiacetonitrile (1.88g, 10mmol) and Intermediate 1 (2.21g, 10mmol). The crude product was recrystallised from ethanol to afford the title compound (1.95g) as a white solid m.p. 164-166°C. (Found: C, 64.88; H, 4.93; N, 3.60. $C_{21}H_{19}Cl_2NO_2$ requires C, 64.96; H, 4.93; N, 3.61%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.85 (1H, br m, OCH_2CH_2), 6.94 (1H, d, \perp 8.4Hz, ArH ortho to OMe), 6.86 (1H, s, $CH=CCN$), 7.1-7.45 (4H, m, ArH para to cyclopentyloxy + $C_6H_3Cl_2$), and 7.75 (1H, d, \perp 1.8Hz, ArH ortho to cyclopentyloxy); m/z 389 (18%), 388 (7), 387 (29), 323 (19), 322 (19), 321 (87), 320 (29), 319 (100), 284 (18), 252 (19), 249 (24), 241 (25), 177 (14), and 41 (33).

35

p) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(3,4-dichlorophenyl) propenenitrile

Fromng 3,4-dichlorophenylacetonitrile (1.88g, 10mmol) and Intermediate 1 (2.23g, 10mmol). The crude product was recrystallised from ethanol to afford the title compound (3.56g, 90%) as a yellow solid m.p. 151.5-154°C (Found: C, 64.89; H, 4.93; N, 3.61. $C_{21}H_{19}Cl_2NO_2$ requires C, 64.96; H, 4.93; N, 3.61%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.82 (1H, br m, $OCHCH_2$), 6.86 (1H, d, J 8.4Hz, ArH ortho to OMe), and 7.2-7.7 (6H, m, 2xArH meta to OMe + $CH=CCN + C_6H_3Cl_2$); m/z 389 (13%), 388 (5), 387 (20), 323 (12), 322 (12), 321 (69), 320 (19), 319 (100), and 41 (21).

q) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2,4-dichlorophenyl) propenenitrile

From 2,4-dichlorophenylacetonitrile (1.90g, 10mmol) and Intermediate 1 (2.21g, 10mmol). The crude product was recrystallised from ethanol to afford the title compound (2.25g) as a white solid m.p. 105-107°C (Found: C, 64.93; H, 4.92; N, 3.64. $C_{21}H_{19}Cl_2NO_2$ requires C, 64.96; H, 4.93; N, 3.61%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.86 (1H, br m, $OCHCH_2$), 6.85 (1H, d, J 8.6Hz, ArH ortho to OMe), 7.05-7.45 (5H, m, ArH para to cyclopentyloxy + $CH=CCN + C_6H_3Cl_2$); and 7.70 (1H, d, J 1.9Hz, ArH ortho to cyclopentyloxy); m/z 389 (12%), 387 (28), 319 (100), 284 (23), 252 (24), 249 (31), and 41 (49)

r) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-trifluoromethyl-phenyl) propenenitrile

From 2-trifluoromethylphenylacetonitrile (1.8g, 10mmol) and Intermediate 1 (2.27g, 10mmoi). Chromatography (SiO_2 ; Et_2O -hexane, 1:2) followed by recrystallisation from ethanol gave the title compound (0.82g) as a white solid m.p. 96-98°C (Found: C, 67.93; H, 5.21; N, 3.53. $C_{22}H_{20}F_3NO_2$ requires C, 68.21; H, 5.20; N, 3.62%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.83 (1H, br m, $OCHCH_2$), 6.85 (1H, d, J 8.4Hz, ArH ortho to OMe), 6.98 (1H,s. $CH=CCN$), 7.18 (1H, dd, J 3.4, 2.2Hz ArH ortho to cyclopentyloxy), 7.25-7.8 (4H, m, $C_6H_4CF_3$), and 7.67 (1H, d, J 2.2Hz ArH ortho to cyclopentyloxy); m/z 387 (M^+ , 17%).

320 (53), 319 (100), 276 (14), 256 (19), 248 (18), 208 (9), 207 (9), and 41 (34).

s) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(3-trifluoromethyl-phenyl)propanenitrile

From 3-trifluoromethylphenylacetonitrile (1.56g, 10mmol) and Intermediate 1 (2.34g, 10.6mmol). Chromatography (SiO₂; Et₂O-hexane, 1:1) gave the title compound (2.62) as a yellow solid m.p. 70-73°C (Found: C, 68.14; H, 5.18; N, 3.55. C₂₂H₂₀F₃NO₂ requires C, 68.21; H, 5.20; N, 3.62%); δH (CDCl₃) 1.5-2.1 (8H, br m, (CH₂)₄), 3.88 (3H, s, OMe), 4.85 (1H, br m, OCH₂CH₂), 6.87 (1H, d, J 8.2Hz, ArH ortho to OMe), 7.29 (1H, dd, J 8.2, 2.1Hz, ArH para to OMe), 7.42 (1H, s, CH=CCN), 7.45-7.85 (4H, m, C₆H₄CF₃), and 7.68 (1H, d, J 2.1Hz, ArH ortho to cyclopentyloxy); m/z 387 (M⁺, 11%), 320 (23), 319 (100), 276 (7), 258 (9), 67 (6), and 41 (21).

t) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-trifluoromethyl-phenyl)propanenitrile

From 4-trifluoromethylphenylacetonitrile (1.85g, 10mmol) and Intermediate 1 (2.36g, 10.7mmol). Chromatography (SiO₂; Et₂O-hexane, 2:1) gave the title compound (3.77g) as a yellow solid m.p. 96-99°C (Found: C, 68.32; H, 5.26; N, 3.38. C₂₂H₂₀F₃NO₂ requires C, 68.21; H, 5.20; N, 3.62%); δH (CDCl₃) 1.5-2.1 (8H, br m, (CH₂)₄), 3.89 (3H, s, OMe), 4.85 (1H, br m, OCH₂CH₂), 6.87 (1H, d, J 8.1Hz, ArH ortho to OMe) and 7.2-7.75 (7H, m, 2xArH meta to OMe + C₆H₄CF₃ + CH=CCN); m/z 387 (M⁺, 14%), 320 (26), 319 (100), 276 (12), 258 (15), and 41 (10).

u) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(3-methoxyphenyl)propanenitrile

From 3-methoxyphenylacetonitrile (1.48g, 10mmol) and Intermediate 1 (2.23g, 10mmol). Chromatography (SiO₂; Et₂O-hexane, 1:1) gave the title compound (1.97g) as a yellow solid m.p. 83-85°C (Found: C, 75.80; H, 6.62; N, 4.13. C₂₂H₂₃NO₃ requires C, 75.62; H, 6.63; N, 4.00%); δH (CDCl₃) 1.5-2.1 (8H, br m, (CH₂)₄), 3.83 (3H, s, OMe), 3.87 (3H, s, OMe), 4.84 (1H, br m, OCH₂CH₂), 6.8-6.95 (3H, m + d (δ6.85, J 7.9Hz), 3 x ArH ortho to OMe), 7.1-7.4 (4H, m, ArH para to OMe + ArH para to cyclopentyloxy + ArH meta to OMe and olefin + CH=CCN) and 7.66 (1H,

d, \downarrow 1.9Hz. ArH ortho to cyclopentyloxy); m/z 349 (M^+ , 27%) 282 (28), 281 (100), 248 (7), 220 (13), and 41 (22).

v) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(3,4-dimethoxyphenyl)propanenitrile

From 3,4-dimethoxyphenylacetonitrile (1.95g, 11mmol) and Intermediate 1 (2.20g, 10mmol). Chromatography (SiO₂; Et₂O-hexane, 1:1) gave the title compound (2.41g) as a yellow solid m.p. 101-103°C. (Found: C, 72.68; H, 6.46; N, 3.49. C₂₃H₂₅NO₃ requires C, 72.80; H, 6.64; N, 3.69%); δH (CDCl₃) 1.5-2.1 (8H, br m, (CH₂)₄), 3.87 (3H, s, OMe), 3.89 (3H, s, OMe), 3.92 (3H, s, OMe), 4.84 (1H, br m, OCH₂CH₂), 6.85 (2H, d, \downarrow 8.1Hz ArH meta to cyclopentyloxy +ArH ortho to OMe), 7.0-7.35 (4H, m, ArH para to cyclopentyloxy + CH=CCN + ArH ortho and ArH para to OMe), and 7.64 (1H, d, \downarrow 2.0Hz, ArH ortho to cyclopentyloxy); m/z 380 (M^+ + 1, 5%), 379 (M^+ , 27), 312 (20), 311 (100), 295 (12), 278 (5), 250 (8), and 41 (8).

w) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2,3,4,5,6-pentafluorophenyl)propanenitrile

From 2, 3, 4, 5, 6-pentafluorophenylacetonitrile (2.07g, 10mmol) and Intermediate 1 (2.20g, 10mmol). The crude product was recrystallised from ethanol to afford the title compound (1.1g) as orange crystals m.p. 94.5-96°C. (Found: C, 61.64; H, 3.94; N, 3.26. C₂₁H₁₆F₅NO₃ requires C, 61.62; H, 3.94; N, 3.42%); δH (CDCl₃) 1.5-2.1 (8H, br m, (CH₂)₄), 3.89 (3H, s, OMe), 4.85 (1H, br m, OCH₂CH₂), 6.85 (1H, d, \downarrow 8.4Hz, ArH ortho to OMe); 7.15 (1H, slightly broadened s, CH=CCN) and 7.23 (1H, dd, \downarrow 8.4, 2.1Hz, ArH para to cyclopentyloxy); m/z 409 (M^+ , 12%), 367 (8), 342 (21), 341 (100), 298 (20), 27(10), 250 (10), and 41 (21).

EXAMPLE 2

a) (Z)-2-(4-Aminophenyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)propanenitrile

A mixture of Intermediate 1 (2.24g, 10mmol), 4-aminophenylacetonitrile (1.37g, 10mmol), and piperidine (10 drops) in ethanol (8ml) was heated to reflux for 6h. The reaction mixture was partitioned between dichloromethane (20ml) and brine (10ml). The organic layer was
5 separated, dried ($MgSO_4$), and concentrated in vacuo. The residue was subjected to chromatography (SiO_2 ; Et_2O -hexane, 2:1) to afford the title compound (1.15g) as a yellow solid m.p. 82-84°C (Found: C, 75.22; H, 6.68; N, 7.86. $C_{21}H_{22}N_2O_2$ requires C, 75.42; H, 6.63; N, 8.38%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.72 (2H, s, $ArNH_2$) 3.88 (3H, s, OMe),
10 4.85 (1H, br m, $OCHCH_2$), 6.87 (1H, d, \downarrow 8.3Hz, ArH ortho to OMe), 7.05-
7.4 (5H, m ArH para to cyclopentyloxy + $C_6H_4NH_2$), 7.52 (1H, d, \downarrow 1.8Hz,
 ArH ortho to cyclopentyloxy) and 8.26 (1H, s, $CH=CCN$); m/z 314 (M^+ ,
79%), 268 (13), 267 (98), 266 (100), 265 (100), 250 (19), 143 (14), 116
(34), 89 (21) and 41 (33).

15

The following compounds were prepared in a manner similar to the compound of Example 2 a.

20 b) (Z)-2-(2-Chlorophenyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)propanenitrile

From 2-chlorophenylacetonitrile (1.53g, 10mmol) and Intermediate 1 (2.23g, 10mmol). Chromatography (SiO_2 ; Et_2O -hexane, 3:2) gave the title compound (1.85g) as pale yellow crystals m.p. 94-95°C (Found: C, 71.25; H, 5.72; N, 3.84. $C_{21}H_{20}ClNO_2$ requires C, 71.28; H, 5.70; N, 3.96%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.85 (1H, br m, $OCHCH_2$), 6.85 (1H, d, \downarrow 8.3Hz, ArH ortho to OMe), 7.11 (1H, s, $CH=CCN$), 7.15-7.5 (5H, m, ArH para to cyclopentyloxy + C_6H_4Cl), and 7.72 (1H, d, \downarrow 2.2Hz, ArH ortho to cyclopentyloxy); m/z 353 (M^+ , 17%),
30 287 (43), 286 (23), 285 (100), 250 (64), 218 (75), 207 (28), 206 (25), 190
(38), and 41 (52).

35 c) (Z)-2-(2-Bromophenyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)propanenitrile

From 2-bromophenylacetonitrile (1.00g, 5.1mmol) and Intermediate 1 (1.13g, 5.1mmol). The crude product was recrystallised from ethanol to

afford the title compound (0.48g) as a white solid m.p. 100-103°C (Found: C, 63.36; H, 5.07; N, 3.51. $C_{21}H_{20}BrNO_2$ requires C, 63.33 H, 5.06; N, 3.52%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.86 (1H, br m, OCH_2CH_2), 6.85 (1H, d, J 8.4Hz, ArH ortho to OMe), 7.06 (1H, s, $CH=CCN$), 7.15-7.4 (45H, m, ArH para to cyclopentyloxy + 2xArH meta to Br + ArH para to Br), 7.5-7.65 (1H, m, ArH ortho to Br), and 7.72 (1H, d, J 1.9Hz, ArH ortho to cyclopentyloxy); m/z 399 (47%), 397 (47), 331 (94), 329 (89), 250 (57), 219 (24), 218 (100), 207 (25), 190 (48), and 41 (36).

10

d) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-nitrophenyl)propanenitrile

From 4-nitrophenylacetonitrile (1.66g 10mmol) and Intermediate 1 (2.20g, 15 10mmol). Chromatography (SiO_2 ; Et_2O -hexane, 1:1) followed by recrystallisation from methanol-ethanol gave the title compound (1.76g) as yellow crystals m.p. 185.5-187°C (Found: C, 69.29; H, 5.40; N, 7.67. $C_{21}H_{20}N_2O_4$ requires C, 69.22; H, 5.53; N, 7.69%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.90 (3H, s, OMe), 4.85 (1H, br m, OCH_2CH_2), 6.88 (1H, d, J 8.5Hz, ArH ortho to OMe), 7.3 (1H, dd, J 8.5, 1.9Hz, ArH para to OMe), 7.52 (1H, s, $CH=CCN$), 7.73 (1H, d, J 1.9Hz, ArH ortho to cyclopentyloxy), 7.75 (2H, ca.d., J 8.7Hz, 2xArH ortho to NO₂); m/z 364 (M⁺, 7%), 297 (28), 296 (100), 266 (29), 207 (13), 206 (10), 190 (10), and 41 (28).

25

e) (Z)-2-(2-Aminophenyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)propanenitrile

From 2-aminophenyiacetonitrile (1.3g, 10mmol) and Intermediate 1 (2.20g, 30 10mmol). Filtration of the reaction mixture gave the title compound (1.75g) as a white solid m.p. 81-82.5°C (Found: C, 74.86; H, 6.63; N, 8.32. $C_{21}H_{22}N_2O_2$ requires C, 75.42; H, 6.63; N, 8.38%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 2.14 (2H, s, NH₂), 3.89 (3H, s, OMe) 4.85 (1H, br m, OCH_2CH_2), 6.88 (1H, d, J 8.4Hz, ArH ortho to OMe), 7.0-7.5 (4H, m, C₆H₄NH₂), 7.30 (1H, dd, J 8.4, 1.9Hz, ArH para to cyclopentyloxy), 7.55 (1H, d, J 1.9Hz, ArH ortho to cyclopentyloxy) and 8.28 (1H, s, $CH=CCN$);

m/z 334 (M⁺, 32%), 266 (41), 265 (97), 252 (12), 251 (65), 250 (26), 249 (100), 69 (11), and 41 (32).

5 f) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-nitrophenyl)propanenitrile

From 2-nitrophenylacetonitrile (1.62g, 10mmol) and Intermediate 1 (2.20g, 10mmol). Chromatography (SiO₂; Et₂O-hexane, 1:1) gave the title compound (2.60g) as a yellow solid m.p. 95.5-97°C (Found: C, 69.14; H, 5.43; N, 7.70. C₂₁H₂₀N₂O₄ requires C, 69.22; H, 5.53; N, 46.69%); δH (CDCl₃) 1.5-2.1 (8H, br m, (CH₂)₄), 3.88 (3H, s, OMe), 4.86 (1H, br m, OCH₂CH₂), 6.8-7.7 (7H, m, 2xArH meta to OMe + ArH ortho to OMe + CH=CCN + 2xArH meta to NO₂ + ArH para to NO₂), and 7.95-8.1 (1H, m, ArH ortho to NO₂); m/z 364 (M⁺, 9%), 332 (19), 296 (33), 265 (20), 264 (100), 250 (12), 249 (35), 225 (10), 221 (17), 152 (60), 151 (26), 69 (16), and 41 (30).

20 EXAMPLE 3

a) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-hydroxyphenyl)propanenitrile

Sodium ethoxide [prepared from sodium (0.35g, 15mmol) in ethanol (10ml)] was added dropwise to a mixture of Intermediate 1 (1.09g, 4.95mmol) and 4-hydroxyphenylacetonitrile (0.67g, 5.03mmol) in ethanol (10ml). The reaction mixture was heated to reflux for 3h then partitioned between dichloromethane (25ml) and saturated sodium hydrogen carbonate solution (15ml). The organic layer was separated, dried (MgSO₄), and concentrated in vacuo. The residue was subjected to chromatography (SiO₂; Et₂O-hexane, 2:3) to afford the title compound (1.57g) as a yellow solid m.p. 138-140°C. (Found: C, 75.16; H, 6.35; N, 4.11. C₂₁H₂₁NO₃ requires C, 75.20; H, 6.31; N, 4.18%); δH (CDCl₃) 1.5-2.0 (8H, br m, (CH₂)₄), 3.86 (3H, s, OMe), 4.85 (1H, br m, OCH₂CH₂), 5.57 (1H, br s, OH), 6.84 (3H, ca. d, J ca. 8.6Hz, ArH ortho to OMe + 2xArH ortho to OH), 7.22 (1H, dd, J 8.4, 1.9Hz, ArH para to OCp), 7.26 (1H, s, CH=CCN), 7.47 (2H, ca. d, J ca. 8.7Hz, 2x ArH meta to OH) and 7.62

(1H, d, \downarrow 8.7Hz, ArH ortho to OCp); m/z 335 (M^+ , 58%), 267 (100), 154 (28), 129 (41), 70 (25), 57 (33), and 41 (40).

The following compounds were prepared in a manner similar to the compound of Example 3 a.

5 b) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-methoxyphenyl)propanenitrile

From 2-methoxyphenylacetonitrile (1.52g, 10mmol) and Intermediate 1

10 (2.21g, 10mmol). The crude product was recrystallised from ethanol to afford the title compound (1.26g) as white crystals m.p. 85-87.5°C (Found: C, 75.67; H, 6.63; N, 3.95. $C_{22}H_{23}NO_3$ requires C, 75.62; H, 6.63; N, 4.01%); δ H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.87 (3H, s, OMe), 3.88 (3H, s, OMe), 4.83 (1H, br m, $OCHCH_2$), 6.83 (1H, d, \downarrow 8.4Hz, 15 ArH ortho to OMe), 6.8-7.4 (5H, m, ArH para to cyclopentyloxy + C_6H_4OMe), 7.25 (1H, s, $CH=CCN$), and 7.70 (1H, d, \downarrow 2.1Hz, ArH ortho to cyclopentyloxy); m/z 350 ($M^+ + 1$, 14%), 349 (M^+ , 57) 282 (20) 281 (100), 150 (12), 129 (37), 71 (11), 70 (11), 67 (13), 57 (16), and 41 (22).

20

c) (Z)-2-(4-Chlorophenyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)propanenitrile

From 4-chlorophenylacetonitrile (1.65g, 8.7mmol) and Intermediate 1

25 (2.00g, 9.1mmol). The crude product was recrystallised from ethanol to afford the title compound (2.74g) as pale yellow crystals m.p. 129-137°C

(Found: C, 71.18; H, 5.69; N, 3.82. $C_{21}H_{20}ClNO_2$ requires C, 71.28; H, 5.70; N, 3.96%); δ H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.85 (1H, br m, $OCHCH_2$), 6.85 (1H, d, \downarrow 8.4Hz, ArH ortho to OMe), 7.2-7.6 (6H, m, ArH para to cyclopentyloxy + $CH=CCN + C_6H_4Cl$),

30 and 7.67 (1H, d, \downarrow 2.1Hz, ArH ortho to cyclopentyloxy); m/z 353 ($M^+ + 10%$), 288 (6), 287 (35), 286 (18), 285 (100), 224 (7), and 207 (10).

35 d) (Z)-2-(4-Bromophenyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)propanenitrile

From 4-bromophenylacetonitrile (2.15g, 10mmol) and Intermediate 1 (2.00g, 9.1mmol). The crude product was recrystallised from ethanol to afford the title compound (3.27g) as yellow crystals m.p. 116-119°C (Found: C, 63.17; H, 5.03; N, 3.35. $C_{21}H_{20}BrNO_2$ requires C, 63.33; H, 5.06; N, 3.52%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.88 (3H, s, OMe), 4.84 (1H, br m, $OCHCH_2$), 6.85 (1H, d, \perp 8.5Hz, ArH ortho to OMe), 7.15-7.35 (1H, m, ArH para to cyclopentyloxy), 7.35 (1H, s, $CH=CCN$), 7.48 (4H, s, C_6H_4CBr), and 7.67 (1H, d, \perp 2.1Hz, ArH ortho to cyclopentyloxy); m/z 399 (16%), 397 (17), 332 (19), 331 (100), 329 (19), 328 (100), 235 (8), 207 (15), and 41 (17).

e) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2,6-dichlorophenyl) propenenitrile

15 From 2,6-dichlorophenylacetonitrile (8.00g, 43mmol) and Intermediate 1 (9.46g, 43mmol). The crude product was recrystallised from ethanol to afford the title compound (12.35g) as a white solid (see Example 1 e) for spectral data).

20

f) (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2,6-dimethoxy-phenyl) propenenitrile

From 2,6-dimethoxyphenylacetonitrile and Intermediate 1. The crude product was recrystallised from ethanol to afford the title compound as white crystals m.p. 120.5-122°C (Found: C, 72.88; H, 6.33; N, 3.13. $C_{23}H_{25}NO_4$ requires C, 77.80; H, 6.64; N, 3.69%); δ_H ($CDCl_3$) 1.45-2.1 (8H, br m, $(CH_2)_4$), 3.84 (6H, s, $C_6H_3(OMe)_2$), 3.89 (3H, s, OMe ortho to cyclopentyloxy), 4.87 (1H, br m, OCH), 6.60 (2H, d, \perp 8.4 Hz, $C_6H_3(OMe)_2$), 6.87 (1H, d, \perp 8.4 Hz, ArH meta to OCp), 7.00 (1H, s, $CH=CCN$), 7.2 (1H, dd, \perp 8.4, 2.1 Hz, ArH para to OCp), 7.29 (1H, d, \perp 8.4Hz, ArH meta to 2 xOMe), and 7.79 (1H, d, \perp 2.1Hz, ArH ortho to OCp); m/z 379 (M⁺, 20%), 312 (21), 311 (100), 280 (11), 152 (43), 151 (72), 150 (33), 137 (18), 91 (16), 85 (15), 83 (23), 43 (10), and 41 (19).

35

EXAMPLE 4

(Z)-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-methoxyphenyl)-propanenitrile

A mixture of the phenol of Example 3 (600mg, 1.79mmol), caesium carbonate (580mg, 1.79mmol), and methyl iodide (0.24mg, 3.8mmol) in

- 5 DMF (10ml) was allowed to stir at ambient temperature for 18h. The reaction mixture was partitioned between dichloromethane (20ml) and saturated sodium hydrogen carbonate solution (10ml). The organic layer was separated, dried (MgSO_4), and concentrated *in vacuo*. The residue was recrystallised from ethanol to afford the title compound (490mg) as
 10 yellow crystals m.p. 102-105°C. (Found: C, 75.43; H, 6.60; N, 3.98. $\text{C}_{22}\text{H}_{23}\text{NO}_3$ requires C, 75.62; H, 6.63; N, 4.01%); δH (CDCl_3) 1.5-2.1 (8H, br m, $(\text{CH}_2)_4$), 3.82 (3H, s, OMe), 3.87 (3H, s, OMe), 4.82 (1H, br m, OCHCH_2), 6.84 (1H, d, \perp ca. 8.6Hz, ArH meta to cyclopentyloxy), 6.89 (2H, ca.d, \perp 8.8Hz, 2x ArH ortho to OMe), 7.23 (1H, dd, \perp 8.6, 2.5Hz, ArH
 15 para to OMe), 7.27 (1H, s, $\text{CH}=\text{CCN}$), 7.53 (2H, ca.d, \perp 8.8Hz, 2x ArH meta to OMe) and 7.64 (1H, d, \perp 2.0Hz, ArH ortho to cyclopentyloxy); m/z 349 (M^+ , 32%), 282 (36), 281 (100), 266 (19), 238 (14), 220 (8), and 41 (11).

20 **EXAMPLE 5**

(E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]-3-nitropyridine

A mixture of Intermediate 1 (2.13g, 9.68mmol), 4-methyl-3-nitropyridine (2.47g, 17mmol), and ammonium acetate (1.19g, 15mmol) in acetic acid (20ml) was heated to reflux for 3h. The reaction mixture was cooled and

- 25 partitioned between dichloromethane (20ml) and saturated sodium hydrogen carbonate solution (2 x 10ml). The organic layer was separated, dried (MgSO_4), and concentrated *in vacuo*. The residue was subjected to chromatography (SiO_2 ; Et_2O -hexane, 1:1) to afford the title compound (1.83g) as an orange solid m.p. 114-116°C. (Found: C, 66.94; H, 5.94; N, 8.01. $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3$ requires C, 67.05; H, 5.92; N, 8.23%); δH (CDCl_3) 1.5-
 30 2.1 (8H, br m, $(\text{CH}_2)_4$), 3.86 (3H, s, OMe), 4.75 (1H, br m, OCHCH_2), 6.84 (1H, d, \perp 8.5Hz, ArH ortho to OMe), 7.0-7.2 (2H, m, 2x ArH meta to OMe)
 35 7.30 (1H, s, $\text{CH}=\text{CH}$), 7.38 (1H, s, $\text{CH}=\text{CH}$), 7.61 (1H, d, \perp 5.4 Hz, pyridine H₅), 8.73. (1H, d, \perp 5.4 Hz, pyridine H₆), and 9.09 (1H, s, pyridine H₂); m/z 340 (M^+ , 15%) 308 (25), 240 (69), 226 (20), 225 (34), 152 (100), 151 (31), 149 (29), 121 (29), 68 (26), 67 (66), and 57 (22).

EXAMPLE 6a) (E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]3,5-dichloropyridine

- 5 Intermediate 3a) (2.65g, 6.92mmol) was dissolved in toluene (60ml) containing p-toluenesulphonic acid (0.2g) and the mixture heated to reflux for 2.5h in a Dean-Stark apparatus. The reaction mixture was concentrated in vacuo and the residue subjected to chromatography
10 (SiO₂; Et₂O-hexane, 1:2) to afford the title compound (1.55g) as yellow crystals m.p. 99-101°C. (Found: C, 62.68; H, 5.22; N, 3.70. C₁₉H₁₉Cl₂NO₂ requires C, 62.65; H, 5.26; N, 3.85%); δ_H (CDCl₃) 1.5-2.1 (8H, br m, (CH₂)₄), 3.86 (3H, s, OMe), 4.82 (1H, br m, OCHCH₂), 6.83 (1H, d, J 8.9Hz, ArH ortho to OMe), 6.90 (1H, d, J 16.6 Hz, CH=CH) 7.0-
15 7.2 (2H, m, 2x ArH meta to OMe), 7.40 (1H, d, J 16.6 Hz, CH=CH), and 8.42(2H, s, pyridine H₂, H₆); m/z 365 (15%), 363 (20), 297 (67), 296 (28), 295 (100), 262 (28), 260 (79), 245 (36), 230 (22), 228 (27), 216 (23), and 152 (24).
- 20 The following compounds were prepared in a manner similar to the compound of Example 6 a.

b) (E)-2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridine

- 25 From Intermediate 3b). The crude product was subjected to chromatography (SiO₂; Et₂O-hexane, 2:1) to afford the title compound (1.58g) as a pale yellow solid m.p. 76-77.5°C. (Found: C, 77.20; H, 7.20; N, 4.63. C₁₉H₂₁NO₂ requires C, 77.26; H, 7.17; N, 4.74%); δ_H (CDCl₃) 1.5-2.1 (8H, br m, (CH₂)₄), 3.84 (3H, s, OMe), 4.80 (1H, br m, OCH), 6.80 (1H, d, J 8.5Hz, ArH ortho to OMe); 6.95 (1H, d, J 15.6 Hz, CH=CH), 6.95-
30 7.7 (5H, m, 2x ArH meta to OMe + pyridine H₃, H₄, H₅), 7.51 (1H, d, J 15.6 Hz, CH=CH), and 8.53(1H, dm, J 4.9 Hz, pyridine H₆); m/z 295 (M⁺, 23%), 294 (11), 227 (21), 226 (100), 211 (18), 184 (10), and 154 (13).

35

c) (E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyrimidine

From Intermediate 3 c). The crude product was subjected to chromatography (SiO_2 ; EtOAc) then recrystallised from Et_2O -hexane to afford the title compound (1.64g) as a pale yellow amorphous solid m.p.

83-84.5°C. (Found: C, 72.58; H, 6.81; N, 9.40. $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_2$ requires C,

- 5 72.95; H, 6.80; N, 9.45%); δH (300MHz; CDCl_3) 1.6-1.7 (2H, br m, cyclopentyl H's), 1.8-2.1 (6H, br m, cyclopentyl H's), 3.90 (3H, s, OMe), 4.84 (1H, br m, OCHCH_2), 6.91 (1H, d, \downarrow 16Hz, $\text{CH}=\text{CH}$), 6.92 (1H, d, \downarrow 8.3 Hz, ArH ortho to OMe), 7.1-7.2 (2H, m, 2x ArH meta to OMe), 7.31 (1H, dd, \downarrow 5.3, 1.3 Hz, pyridine H₅), 7.81 (1H, d, \downarrow 16 Hz, $\text{CH}=\text{CH}$), 8.65 (1H, d, \downarrow 5.3 Hz, pyridine H₆), and 9.14 (1H, d, \downarrow 1.3Hz, pyridine H₂); m/z 296 (M^+ , 18%), 228 (26), 227 (100), 213 (6), 212 (7), and 41 (9).

EXAMPLE 7

a) (E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridazine

- 15 Intermediate 4a) was dissolved in toluene (50ml) containing 4-toluenesulphonic acid (0.1g) and the mixture heated to reflux in a Dean-Stark apparatus for 2h. The cooled reaction mixture was poured into saturated sodium hydrogen carbonate solution (25ml) and extracted with dichloromethane (1x50ml, 1x25ml). The organic extract was dried (MgSO_4), concentrated in vacuo and the residue subjected to chromatography (SiO_2 ; Et_2O -hexane, 1:1) to afford the title compound (370mg). (Found: C, 72.75; H, 6.78; N, 9.23. $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_2$ requires C, 72.95; H, 6.80; N, 9.45%); δH (CDCl_3) 1.5-2.1 (8H, br m, $(\text{CH}_2)_4$), 3.85 (3H, s, OMe), 4.82 (1H, br m, OCH), 6.75-7.7 (7H, br m, ArH ortho to OMe + 2x ArH meta to OMe + $\text{CH}=\text{CH}$ + pyridazine H₃, H₅), 8.95 (1H, dd, \downarrow 4.3, 1.4 Hz, pyridazine H₆);

The following compounds were prepared in a manner similar to the compound of Example 7a.

- 30 b) (E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridine
From Intermediate 4b). The crude product was subjected to chromatography (SiO_2 ; EtOAc) to afford the title compound (7.47g) as pale yellow needles m.p. 108-108.5°C (from Et_2O -hexane). (Found: C, 76.92; H, 7.12; N, 4.88. $\text{C}_{19}\text{H}_{21}\text{NO}_2$ requires C, 77.26; H, 7.17; N, 4.74%); δH (CDCl_3) 1.5-2.1 (8H, br m, $(\text{CH}_2)_4$), 3.84 (3H, s, OMe), 4.81

(1H, br m, OCH₂CH₂), 6.77 (1H, d, \downarrow 15.8 Hz, CH=CH), 6.81 (1H, d, \downarrow ca. 9 Hz, ArH ortho to OMe), 6.95-7.1 (3H, m, ArH meta to OMe + CH=CH), 7.28 (2H, dd, \downarrow 4.7, 1.6 Hz, pyridine H₃, H₅), and 8.49 (2H, dd, \downarrow 4.7, 1.6 Hz, pyridine H₂, H₆); m/z 295 (M⁺, 35%), 228 (20), 227 (100), 226 (86), 5 198 (34), 184 (23), 167 (12), 166 (16), 154 (10), and 41 (20).

c) (E)-2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyrazine

From Intermediate 4c). The crude product was subjected to chromatography (SiO₂; Et₂O-hexane, 1:1) to afford the title compound

10 (0.80g) as a pale brown solid m.p. 81-83°C. (Found: C, 72.94; H, 6.78; N, 9.23. C₁₈H₂₀N₂O₂ requires C, 72.94; H, 6.80; N, 9.45%); δH (CDCl₃) 1.5-2.0 (8H, br m, (CH₂)₄), 3.84 (3H, s, OMe), 4.80 (1H, br m, OCH₂), 6.81 (1H, d, \downarrow 8.8 Hz, ArH ortho to OMe), 6.93 (1H, d, \downarrow 15.9 Hz, CH=CH), 7.0-7.15 (2H, m, 2xArH meta to OMe), 7.63 (1H, d, \downarrow 15.9 Hz, CH=CH), and 8.25-15 8.60 (3H, m, pyrazine H₃, H₅, H₆).

d) (E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-1-propenyl]pyridine

From Intermediate 7 (1g) using 10% NaOH solution (25ml).

20 Chromatography (SiO₂; dichloromethane) followed by recrystallisation (hexane) afforded a mixture of (Z)- title compound, 4-[2-{1-(3-Cyclopentyloxy-4-methoxyphenyl)propenyl}pyridine, and the title compound (247mg) as white needles m.p. 78-79°C. Found C, 77.64; H, 7.58; N, 4.41 C₂₀H₂₃NO₂ requires C, 77.63; H, 7.49; N, 4.52%). δH (80 MHz; CDCl₃) 1.6-2.0 (8H, br m, (CH₂)₄), 2.26 (3H, d, \downarrow 1.3Hz, CH₃), 3.85 (3H, s, OMe), 4.75-4.86 (1H, m, OCH₂CH₂), 6.60-7.21 (6H, m, ArH + PyH₃, H₅ + C=CH), and 8.52 (2H, br d, PyH₂, H₆). m/z (EI) 309 (M⁺, 30%), 241 (100), 222 (21), and 212 (29).

30 e) (E)-4-[2-{1-(3-Cyclopentyloxy-4-methoxyphenyl)-1-propenyl}pyridine hydrochloride

From Intermediate 3d (0.40g, 1.22mmol). Purification by column chromatography (SiO₂; EtOAc) afforded the title compound free base which was dissolved in Et₂O and treated with ethanolic HCl to give the title

35 compound as a fine yellow precipitate. m.p. 197.1 - 200.6°C. (Found: C, 69.12; H, 6.92; N, 3.96 C₂₀H₂₃NO HCl requires C, 69.45; H, 6.99; N,

4.05%). δ H (80 MHz; CDCl₃) 1.6-2.0 (8H, br m, (CH₂)₄), 2.39 (3H, d, \perp 1.0Hz, CH₃), 3.87 (3H, s, OCH₃), 4.73-4.83 (1H, m, OCH=CH₂), 6.93-7.0 (3H, m, ArH), 7.25 (1H, s, HC=C), 7.90 (2H, br d, PyH₃, H₅), and 8.65 (2H, br d, PyH₂, H₆). m/z (EI) 309 (M⁺-HCl), 241 and 212.

5

EXAMPLE 8

(Z)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridine

A solution of sodium ethoxide [prepared from sodium (0.10g, 4.50mmol)] in ethanol (50ml) was added over 5 min to a stirred mixture of 4-pyridine carboxaldehyde (0.44g, 4.10mmol) and (3-cyclopentyloxy-4-methoxyphenyl)-methyltriphenylphosphonium chloride (2.00g, 4.08g) in ethanol (30ml). After 2h, the reaction mixture was concentrated in vacuo and the residue partitioned between EtOAc (75ml) and brine (50ml). The organic layer was separated, then dried (MgSO₄) and concentrated in vacuo. A ¹H n.m.r. spectrum indicated that the mixture consisted of a 3:2 mixture of (Z) : (E) title compound (and triphenylphosphine oxide). A portion (0.6g) of the mixture was subjected to chromatography (SiO₂; hexane to EtOAc) to afford pure (Z)-title compound (0.14g) as a pale yellow solid m.p. (Found: C, 77.18; H, 7.16; N, 4.63. C₁₉H₂₁NO₂ requires C, 77.26; H, 7.17; N, 4.74%); δ H (300MHz; CDCl₃) 1.5-1.55 (2H, br m, cyclopentyl H's), 1.65-1.9 (6H, br m, cyclopentyl H's), 3.83 (3H, s, OMe), 4.44 (1H, br m, OCH=CH₂), 6.40 (1H, d, \perp 12.2 Hz, CH=CH), 6.65-6.80 (4H, m, ArH ortho to OMe + 2xArH meta to OMe + CH=CH), 7.15 (2H, \perp d, \perp 6.0 Hz, pyridine H₂, H₆); m/z 295 (M⁺, 22%), 228 (15), 227 (100), 226 (94), 198 (35), 184 (15), 166 (12), 43 (19), and 41 (29).

EXAMPLE 9

(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(phenylmethyl)propanenitrile

30 A solution of Intermediate 5 (1.1g) in toluene (100ml) containing 4-toluenesulfonic acid (0.05g) was heated to reflux for 3h. The reaction mixture was partitioned between saturated sodium hydrogen carbonate solution (50ml) and dichloromethane (50ml). The organic phase was separated then dried (MgSO₄) and concentrated in vacuo. The residue was subjected to chromatography (SiO₂; Et₂O-hexane, 1:1) to afford the title compound (0.90g) as an off-white solid m.p. 111-112°C. (Found: C,

35

79.12; H, 7.00; N, 4.13. $C_{22}H_{23}NO_2$ requires C, 79.25; H, 6.95; N, 4.20%); δ_H ($CDCl_3$) 1.5-2.1 (8H, br m, $(CH_2)_4$), 3.64 (2H, d, $\perp 0.9Hz$, $PhCH_2$), 3.83 (3H, s, OMe), 4.85 (1H, br m, OCH $_2$ CH $_2$), 6.78 (1H, d, $\perp 8.3Hz$, ArH ortho to OMe), 6.82 (1H, d, $\perp 0.9Hz$, CH=CCN), 7.07 (1H, dd, $\perp 8.6, 2.0Hz$, ArH para to cyclopentyloxy), 7.2-7.3 (5H, ca. s, C_6H_5), and 7.50 (1H, d, $\perp 1.8Hz$, ArH ortho to cyclopentyloxy); m/z 333 (M^+ , 16%), 266 (19), 265 (100), 264 (25), 222 (11), 137 (11), 115 (14), and 41 (13).

EXAMPLE 10

10 **(E) and (Z) Isomers of 3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4,5-dichloro-1-imidazolyl) propenenitrile**

4,5-dichloroimidazol-1-yl acetonitrile (purified by dissolution in CH_2Cl_2 , containing florisil and SiO_2) (2.99g, 0.016mol) in THF (5ml) was added to a solution of LDA [made from diisopropylamine (190ml, 0.0135mol) and n-butyllithium (10.60ml)] in THF at 0°C. The reaction mixture was stirred at 0°C. for ca 30min, filtered and concentrated to dryness. Purification by column chromatography (SiO_2 ; EtOAc-hexane, 1:3) gave (1) (Z) title compound (0.218g) after trituration in hexane as a yellow solid m.p. 87.8-88.8 (Found: C, 57.05; H, 4.48; N, 10.96 $C_{18}H_{17}O_2N_3Cl_2$ requires C, 57.16; H, 4.53; N, 11.11%). δ_H (80MHz; $CDCl_3$) 1.5-2.0 (8H, br m, $(CH_2)_4$), 3.84 (3H, s, OCH $_3$), 4.3-4.4 (1H, m, OCH $_2$ CH $_2$), 6.00 (1H, s, ArH), 6.77 (2H, br s, ArH), 7.33 (1H, s, HC=C or imid CH), and 7.42 (1H, s, HC=C or imid CH). m/z (EI) 379 (M^+ , 3%), 377 (5), 308 (10), 276 (11), 275 (13), 274 (41), 273 (28), 247 (11), 242 (100), 230 (22), and 214 (10).

25

(2) (E) title compound (0.189g) as pale yellow crystals m.p. 129.3-131.9 (from EtOH). (Found: C, 57.08; H, 4.48; N, 10.92 $C_{18}H_{17}O_2N_3Cl_2$ requires C, 57.16; H, 4.53; N, 11.11%) δ_H (80 MHz; $CDCl_3$) 1.6-2.0 (8H, br m, $(CH_2)_4$), 3.91 (3H, s, OCH $_3$), 4.78-4.86(1H, m, OCH $_2$ CH $_2$), 6.88 (1H, d, $\perp 8.5Hz$, ArH $_5$), 7.15-7.3 (2H, m, ArH), 7.51 (1H, s, imid CH), and 7.60 (1H, d, $\perp 2.0Hz$, HC=C). m/z (EI) 379 (M^+ , 63%), 377 (88), 311 (27), 310 (12), 309 (39), 276 (33), 275 (27), 274 (96), 273 (35), and 242 (100).

35 **EXAMPLE 11**

(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)2-(2,6-difluorophenyl)propanenitrile

To a solution of LDA [made from butyllithium (6.70ml, 0.010mol) and diisopropylamine (1.80ml, 0.012mol)] in THF at -10°C was added 2,6-

- 5 difluorophenylacetonitrile (1.20ml, 9.70mmol). The solution became yellow. Left to stir at -10°C for ca 30min before adding chlorotrimethylsilane (1.30ml, 0.010mol). The solution became colourless. Left to stir at -10°C for ca 20min before cooling to -78°C and adding butyllithium (6ml; 9.6mmol)). The solution became light orange. Left to 10 stir ca 15 min before adding Intermediate 1 (2.13g, 9.68mmol). The reaction mixture was left to warm to RT overnight, washed with saturated sodium bicarbonate solution, extracted with dichloromethane, dried (MgSO₄) and concentrated *in vacuo*. Chromatography (SiO₂; Et₂O-hexane, 1:4) afforded the title compound (0.301g) as white crystals. m.p. 15 79.1-81°C (Found C, 70.80; H, 5.39; N, 3.93. C₂₁H₁₉F₂NO₂ requires C, 70.97; H, 5.39; N, 3.94%). δH (80MHz; CDCl₃) 1.5-2.0 (8H, br m, (CH₂)₄), 3.88 (3H, s, OCH₃), 4.18-4.9 (1H, m, OCHCH₂), 6.78-7.4 (6H, m, ArH + HC=C), and 7.74 (1H, d, J 2.1Hz, ArH). m/z (EI) 355 (M⁺, 15%), 287 (100), 244 (15) and 84 (25).

20

EXAMPLE 12

Ethyl cis-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)propanoate

A mixture of Intermediate 1 (26.62g; 0.12mol), ethyl-4-pyridylacetate

- 25 (19.92g; 0.12mol; 1eq) and ammonium acetate (18.63g; 0.24g; 2eq) in glacial acetic acid (200ml) was stirred at 120°C under N₂ for 20 hours. The solution was cooled to room temperature and the acid removed *in* vacuo to give an orangey/brown residue. This residue was taken up in a saturated bicarbonate solution (to pH=8.5) and extracted several times 30 with ethyl acetate. The combined organic layer was washed with brine, dried (MgSO₄) and evaporated to dryness to give a yellow solid. Recrystallisation from toluene/hexane (1st crop) then toluene (2nd crop) followed by column chromatography (SiO₂; hexane-EtOAc/hexane: 7/3) gave the title compound m.p. 109-111°C as a white crystalline solid. δH (CDCl₃) 1.27 (3H, t, J 7.1 Hz, CH₂CH₃), 1.45-1.8 (8H, br m, cyclopentyl H's), 3.81 (3H, s, OMe), 4.16 (1H, br m, OCH), 4.25 (2H, q, J 7.1 Hz,
- 35

CH_2CH_3), 6.43 (1H, d, \downarrow 2.0Hz, ArH *ortho* to cyclopentyloxy), 6.73 (1H, d, \downarrow 8.4 Hz, ArH *ortho* to OMe), 6.80 (1H, dd, \downarrow 2.0, 8.4 Hz, ArH *para* to cyclopentyloxy), 7.22 (2H, dd, \downarrow 1.6, 4.5 Hz, pyridine H₃, H₅), 7.83 (1H, s, HC = C) and 8.64 (2H, dd, \downarrow 1.6, 4.5 Hz, pyridine H₂, H₆).

5 An alternative procedure is as follows:

To a stirred solution of Intermediate 1 (22g; 100mmol) and ethyl-4-pyridyl-acetate (16.5g; 100mmol) in dry toluene (150ml) at room temperature was added glacial acetic acid (2.4ml) followed by piperidine (0.8ml). The solution was heated to reflux and the water produced removed as an azeotrope, collected by a Dean Stark Apparatus. After 16 hrs, the solution was allowed to cool to room temperature, charcoal and Florisil added, stirred for 5 minutes and then filtered. The solvent was removed by evaporation *in vacuo*. The crystalline solid obtained was dissolved in dichloromethane, washed with a saturated sodium bicarbonate solution, dried (MgSO_4), filtered and the solvent removed by evaporation *in vacuo*. The product was recrystallised (diisopropyl ether) to give the title compound as a white crystalline solid, with melting point and NMR consistent with the above values.

20 **EXAMPLE 13**

(E)-1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(3-pyridyl)ethene

Potassium *tert*-butoxide (197mg, 1.75mmol, 1.2eq) was added to a solution of Intermediate 10(500mg, 1.46mmol) in THF at 0°C. The mixture was stirred for 5 min then a solution of 3-pyridinecarboxaldehyde (156mg, 1.46mmol) in THF (5ml) was added dropwise. After stirring at RT for 16h the reaction mixture was concentrated *in vacuo*. The residue was partitioned between chloroform (10ml) and water (5ml), and the organic phase was separated, dried (MgSO_4), and concentrated *in vacuo*. The residue was subjected to chromatography (SiO_2 ; EtOAc-hexane, 1:1) to afford the title compound (196mg) as a pale yellow oil; δ_{H} (80MHz; CDCl_3) 1.5-2.1 (8H, br m, $(\text{CH}_2)_4$), 3.82 (3H, s, OMe), 4.80 (1H, br m, OCH), 6.7-7.3 (6H, m, $\text{C}_6\text{H}_3 + \text{HC}=\text{CH} + \text{pyridine H}_4$), 7.73 (1H, m, pyridine H₅), 8.40 (1H, dd, \downarrow 4.5, 2.0Hz, pyridine H₆), and 8.64 (1H, d, \downarrow 2.0Hz, pyridine H₂).

The title compound (185mg) was dissolved in ethanol (5ml) and treated with Et₂O-HCl. The mixture was concentrated *in vacuo* and the residue recrystallised from chloroform-hexane to afford the title compound hydrochloride (173mg) as pale yellow crystals m.p. 177-181°C (300MHz;

- 5 CDCl₃) 1.65-2.1 (8H, br m, (CH₂)₄), 3.91 (3H, s, OMe), 4.87 (1H, br.m, OCH), 6.91 (1H, d, J 8.0 Hz, ArH *ortho* to OMe), 6.93 (1H, d, J 16.2Hz, CH=CH), 7.05-7.15 (2H, m, 2 x ArH *meta* to OMe), 7.2-7.3 (1H, m, pyridine H₄), 7.73 (1H, d, J 16.2Hz, CH=CH), 7.85 (1H, dd, J 7.5, 5.0Hz, pyridine H₅), 8.41 (1H, d, J 7.5Hz, pyridine H₆), 8.55 (1H, d, J 5.0Hz, pyridine H₂), and 8.87 (1H, br s, NH); m/z (EI) 295 (M⁺-HCl, 49%), 228 (20), 227 (100), 226 (92), 207 (28), 198 (25), 180 (39), 41 (34), 38 (27), and 36 (85).

15 **FORMULATION EXAMPLES**

The compounds of the invention may be formulated for pharmaceutical use in a number of forms using any suitable excipients. Thus, for example, for oral use the compounds of the invention such as the compounds of the Examples may be formulated as a solid dosage form,

- 20 by mixing an appropriate weight of compound (for example 50mg) with maize starch (50-99%w/w), anhydrous colloidal silica (0-10%w/w) and organic or inorganic acid (up to 1%w/w), to fill capsules of an appropriate size, e.g. white opaque hard gelatine capsules size 3. If desired the same mixture may be compressed into tablets.

25

The activity and selectivity of compounds according to the invention was demonstrated in the following tests. In these tests the abbreviation FMLP represents the peptide N-formyl-met-leu-phe.

30 **Isolated Enzyme**

The potency and selectivity of the compounds of the invention was determined using distinct PDE isoenzymes as follows:

- 35 i. PDE I, rabbit heart
ii. PDE II, rabbit heart
iii. PDE III, rabbit heart, Jurkat cells

- iv. PDE IV, HL60 cells, rabbit brain, rabbit kidney and human recombinant PDE IV
 - v. PDE V, rabbit lung, guinea pig lung
- 5 A gene encoding human PDE IV has been cloned from human monocytes (*Livi, et al.*, 1990, *Molecular and Cellular Biology*, 10, 2678). Using similar procedures we have cloned human PDE IV genes from a number of sources including eosinophils, neutrophils, lymphocytes, monocytes, brain and neuronal tissues. These genes have been transfected into yeast
- 10 10 using an inducible vector and various recombinant proteins have been expressed which have the biochemical characteristics of PDE IV (*Beavo and Reifsnyder*, 1990, *TIPS*, 11, 150). These recombinant enzymes, particularly the human eosinophil recombinant PDE IV, have been used as the basis of a screen for potent, selective PDE IV inhibitors.
- 15 15 The enzymes were purified to isoenzyme homogeneity using standard chromatographic techniques.
- 20 Phosphodiesterase activity was assayed as follows. The reaction was conducted in 150 μ l of standard mixture containing (final concentrations): 50mM 2-[tris(hydroxymethyl)methyl]amino]-1-ethane-sulphonic acid (TES)-NaOH buffer (pH 7.5), 10mM MgCl₂, 0.1 μ M [³H]-cAMP and vehicle or various concentrations of the test compounds. The reaction was initiated by addition of enzyme and conducted at 30°C for between 5 to 30 min.
- 25 25 The reaction was terminated by addition of 50 μ l 2% trifluoroacetic acid containing [¹⁴C]-5'AMP for determining recovery of the product. An aliquot of the sample was then applied to a column of neutral alumina and the [³H]-cAMP eluted with 10ml 0.1 TES-NaOH buffer (pH8). The [³H]-5'-AMP product was eluted with 2ml 2M NaOH into a scintillation vial containing
- 30 30 10ml of scintillation cocktail. Recovery of [³H]-5'AMP was determined using the [¹⁴C]-5'AMP and all assays were conducted in the linear range of the reaction.
- 35 Compounds according to the invention such as compounds of the Examples herein cause a concentration-dependent inhibition of

recombinant PDE IV at 0.1 - 1000nM with little or no activity against PDE I, II, III or V at concentrations up to 100 μ M.

2. The Elevation of cAMP in Leukocytes

5 The effect of compounds of the invention on intracellular cAMP was investigated using human neutrophils or guinea pig eosinophils. Human neutrophils were separated from peripheral blood, incubated with dihydrocytochalasin B and the test compound for 10 min and then stimulated with FMLP. Guinea pig eosinophils were harvested
10 by peritoneal lavage of animals previously treated with intra-peritoneal injections of human serum. Eosinophils were separated from the peritoneal exudate and incubated with isoprenaline and test compound. With both cell types, suspensions were centrifuged at the end of the incubation, the cell pellets were resuspended in buffer and boiled for 10 min prior to measurement of cAMP by specific
15 radioimmunoassay (DuPont).

20 The most potent compounds according to the Examples induced a concentration-dependent elevation of cAMP in neutrophils and/or eosinophils at concentrations of 0.1nM to 1 μ M.

3. Suppression of Leukocyte Function

25 Compounds of the invention were investigated for their effects on superoxide generation, chemotaxis and adhesion of neutrophils and eosinophils. Isolated leukocytes were incubated with dihydrocytochalasin B for superoxide generation only and test compound prior to stimulation with FMLP. The most potent compounds of the Examples caused a concentration-dependent inhibition of superoxide generation, chemotaxis and adhesion at concentrations of 0.1nM to
30 1 μ M.

Lipopolysaccharide (LPS)-induced synthesis of tumour necrosis factor (TNF) by human peripheral blood monocytes (PBM) is inhibited by compounds of the Examples at concentrations of 0.01nM to 10 μ M.

4. Relaxation of Constricted Airway Smooth Muscle In vitro

The effects of compounds of the invention on guinea-pig isolated tracheal smooth muscle were investigated. Isolated tracheal rings were suspended in organ baths and immersed in oxygenated Krebs' solution. The smooth muscle was contracted with sub-maximal concentrations of histamine or carbachol prior to the addition of increasing concentrations of test compound to the organ baths. The most potent compounds of the Examples caused a concentration-dependent reversal of both histamine and carbachol-induced contractions at concentrations of 1nM to 100 μ M. The compounds were generally more potent in reversing histamine-induced tone than carbachol-induced tone.

5. Effects on Cardiac Muscle In vitro

Compounds of the invention have been tested for their effects on isolated cardiac muscle. Right atrial and papillary muscles were dissected out from the hearts of guinea pigs and suspended in organ baths for measuring the rate (chronotropic) of spontaneously beating atria and force (inotropic) of the electrically stimulated papillary muscle. In these preparations, selective PDE IV inhibitors such as rolipram do not have any direct effects whereas selective PDE III inhibitors such as milrinone have positive chronotropic and inotropic effects. The non-specific PDE inhibitor theophylline, which is used in asthma as a bronchodilator, also causes significant cardiovascular changes such as tachycardia. Selective PDE IV inhibitors have advantage over theophylline, therefore, through reduced cardiovascular side effects. The most potent and selective compounds of the Examples had no direct effects on the atrial and papillary muscles in vitro at concentrations up to 10 μ M but in combination with PDE III inhibitors, these inhibitors showed an enhancement of chronotropic and inotropic activity, typical of selective type IV inhibitors.

35 6. Anti-inflammatory Activity in vivo

Interleukin-5 (IL-5)-induced pleural eosinophilia in the rat (*Lisle, et al., 1993, Br.J. Pharmacol. 108, 230*) is inhibited by compounds of the

Examples given orally at doses of 0.0001 to 10.0mg/kg. The most potent compounds cause a dose-dependent reduction in migrating eosinophils with ED₅₀s of 0.003 to 0.03mg/kg p.o.

5 Compounds of the invention also reduce the inflammatory responses induced in rats by platelet activating factor (PAF).

7. Anti-allergic Activity in vivo

10 Compounds of the invention have been tested for effects on an IgE-mediated allergic pulmonary inflammation induced by inhalation of antigen by sensitised guinea pigs. Guinea pigs were initially sensitised to ovalbumin under mild cyclophosphamide-induced immunosuppression, by intraperitoneal injection of antigen in combinations with aluminium hydroxide and pertussis vaccine.
15 Booster doses of antigen were given two and four weeks later and at six weeks, animals were challenged with aerosolised ovalbumin whilst under cover of an intraperitoneally administered anti-histamine agent (mepyramine). After a further 48h, bronchial alveolar lavages (BAL) were performed and the numbers of eosinophils and other leukocytes in the BAL fluids were counted. The lungs were also removed for histological examination for inflammatory damage.
20 Administration of compounds of the Examples (0.001-10mg/kg i.p. or p.o.), up to three times during the 48h following antigen challenge, lead to a significant reduction in the eosinophilia and the accumulation of other inflammatory leukocytes. There was also less inflammatory damage in the lungs of animals treated with compounds of the Examples.

30 8. Effects on Pulmonary Dynamics

Compounds of the invention (0.001-10mg/kg by oral or other route of administration) reduce the allergic bronchoconstriction caused by antigen in sensitized guinea pigs.

35 Compounds of the invention have been tested for their effects on ozone-induced hyperreactivity of the airways of guinea pigs. Following the inhalation of ozone, guinea pigs become very much

more sensitive to the bronchoconstrictor effects of inhaled histamin than naive animals (*Yeadon et al.* 1992, *Pulmonary Pharm.*, 5, 39). There is a pronounced shift to the left (10-30 fold) of the dose response curve to histamine and a highly significant increase in the maximum increase in pulmonary resistance. Compounds of the Examples administered 1h prior to ozone by the intraperitoneal or oral (0.001-10mg/kg) route caused a dose-dependent inhibition of ozone-induced hyperreactivity.

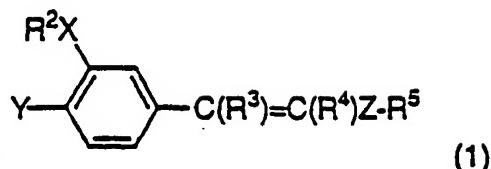
10 9. **Adverse Effects**

In general, in our tests above, compounds of the invention have had no observed toxic effects when administered to animals at the doses shown.

CLAIMS

1. A compound of formula (1)

5



wherein

Y is a halogen atom or a group -OR¹, wherein R¹ is an optionally substituted alkyl group;

10

X is -O-, -S-, or -N(R⁶)-, wherein R⁶ is a hydrogen atom or an optionally substituted alkyl group;

R² is an optionally substituted cycloalkyl or cycloalkenyl group;

15

R³ and R⁴ which may be the same or different, is each a hydrogen atom or an optionally substituted alkyl, -CO₂R⁷ (wherein R⁷ is a hydrogen atom, an optionally substituted alkyl, aralkyl or aryl group), -CONR⁸R⁹ (wherein R⁸ and R⁹, which may be the same or different, is as defined for R⁷), -CSNR⁸R⁹, -CN or -CH₂CN group;

Z is -(CH₂)_n- where n is zero or an integer 1, 2 or 3;

20

R⁵ is an optionally substituted monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms;

and the salts, solvates, hydrates, prodrugs and N-oxides thereof.

- 25 2. A compound according to Claim 1 wherein Y is a -OR¹ group.

3. A compound according to Claim 2 wherein R¹ is an optionally substituted straight or branched C₁₋₃alkyl group.

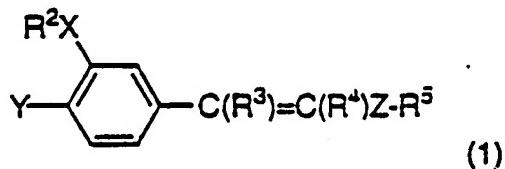
- 30 4. A compound according to Claim 3, where R¹ is a methyl group.

5. A compound according to any of Claims 1 to 4, wherein X is -O-.

6. A compound according to any of Claims 1 to 5 wherein R² is a cyclopentyl group.
7. A compound according to any of Claims 1 to 6 wherein Z is a -(CH₂)_n group wherein n is zero, or an integer 1 or 2.
8. A compound according to Claim 7 wherein Z is a -(CH₂)_n- group where n is zero.
- 10 9. A compound according to any of Claims 1 to 8 wherein R³ is a hydrogen atom or a -CH₃ group.
10. A compound according to Claim 9 where R³ is a hydrogen atom.
- 15 11. A compound according to any of Claims 1 to 10 wherein R⁴ is a hydrogen atom or an optionally substituted alkyl or -CN group.
12. A compound according to Claim 11 wherein R⁴ is a hydrogen atom or a -CN group.
- 20 13. A compound according to any of Claims 1 to 12 wherein R⁵ is an optionally substituted C₆-12aryl group or a C₃-heteroaryl group containing one, two, or three heteroatoms selected from -O-, -S- or -N- atoms.
- 25 14. A compound according to Claim 13 where R⁵ is an optionally substituted phenyl, pyridyl, thienyl, imidazolyl, pyridazinyl or pyrimidinyl group.
- 30 15. A compound according to Claim 14 where R⁵ is an optionally substituted phenyl or pyridyl group.
16. A compound according to Claim 15 where R⁵ is a phenyl or a 2- or 3- monosubstituted or 2,6-disubstituted phenyl group.

17. A compound according to Claim 15 where R⁵ is a 2-, 3- or 4-pyridyl group or a 3,5 disubstituted 4-pyridyl group.
18. A compound according to any of Claims 13 to 17 wherein the aryl or heteroaryl group is substituted by one or two R¹⁰ substituents, where R¹⁰ is an atom or group R¹¹ or -Alk¹(R¹¹)_m wherein R¹¹ is a halogen atom, or an amino (-NH₂), substituted amino, nitro, cyano, hydroxyl (-OH), substituted hydroxyl, cycloalkoxy, formyl [HC(O)-], carboxyl (-CO₂H), esterified carboxyl, thiol (-SH), substituted thiol, -C(O)R^{7a}, [where R^{7a} is a hydrogen atom or an optionally substituted alkyl, aralkyl or aryl group], -SO₃H, -SO₂R^{7a}, SO₂N(R^{7a}R^{8a}), (where R^{8a} is as defined for R^{7a} and may be the same as or different to R^{7a}) -CON[R^{7a}R^{8a}], -NHSO₂R^{7a}, -N(SO₂R^{7a}R^{8a}), -NHSO₂N(R^{7a}R^{8a}), -NHC(O)R^{7a}, or -NHC(O)OR^{7a} group; Alk¹ is a straight or branched C₁-alkylene, C₂-alkenylene, or C₂-alkynylene chain optionally interrupted by one, two, or three -O-, or -S- atoms or -S(O)p-, [where p is an integer 1 or 2] or -N(R⁶)-(where R⁶ is a hydrogen atom or an optionally substituted alkyl group) groups; and m is zero or an integer 1, 2 or 3.
19. A compound according to Claim 18 wherein R¹⁰ is a halogen atom or a nitro, amino, alkoxy, haloalkyl, hydroxy, -NHCOR^{7a}, -NHCONHR^{7a}, or -NHSO₂R^{7a} group.
20. A compound which is
(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-hydroxyphenyl)propanenitrile;
(E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridine;
(Z)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridine;
(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-nitrophenyl)propanenitrile;
(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)2-(4,5-dichloro-1-imidazolyl)propanenitrile;
(Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)propanenitrile;

- (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2-thienyl)propenenitrile;
- (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2,6-difluorophenyl)propenenitrile;
- 5 (E)-4-[2-{1-(3-Cyclopentyloxy-4-methoxy)phenyl}-1-propenyl]pyridine;
- (E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]-3,5-dichloropyridine;
- 10 (Z)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(2,6-dichlorophenyl)propenenitrile;
- N-[4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]-3-pyridyl]phenylsulphonamide;
- (E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]-3-nitropyridine;
- 15 (E)-2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridine;
- (E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyrimidine; or
- (E)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]pyridazine;
- and the salts, solvates, hydrates and N-oxides thereof.
- 20 21. A pharmaceutical composition comprising a compound of formula (1)



- 25 wherein
- Y is a halogen atom or a group -OR¹, wherein R¹ is an optionally substituted alkyl group;
- X is -O-, -S-, or -N(R⁶)-, wherein R⁶ is a hydrogen atom or an optionally substituted alkyl group;
- 30 R² is an optionally substituted cycloalkyl or cycloalkenyl group;
- R³ and R⁴ which may be the same or different, is each a hydrogen atom or an optionally substituted alkyl, -CO₂R⁷ (wherein R⁷ is a hydrogen atom, an optionally substituted alkyl, aralkyl or aryl

group), -CONR⁸R⁹ (wherein R⁸ and R⁹, which may be the same or different, is as defined for R⁷), -CSNR⁸R⁹, -CN or -CH₂CN group; Z is -(CH₂)_n- where n is zero or an integer 1, 2 or 3; R⁵ is an optionally substituted monocyclic or bicyclic aryl group 5 optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms; and the salts, solvates, hydrates, prodrugs and N-oxides thereof, together with one or more pharmaceutically acceptable carriers, excipients or diluents.

10

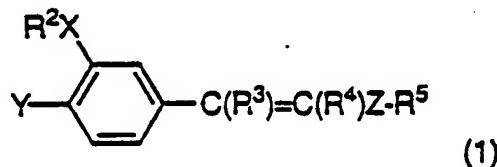
22. A composition according to Claim 21 in a form suitable for oral administration.

15

23. A composition according to Claim 22 where the form for oral administration is a tablet, lozenge or capsule.

24. A process for the preparation of a compound of formula (1)

20



wherein

Y is a halogen atom or a group -OR¹, wherein R¹ is an optionally substituted alkyl group;

25

X is -O-, -S-, or -N(R⁶)-, wherein R⁶ is a hydrogen atom or an optionally substituted alkyl group;

R² is an optionally substituted cycloalkyl or cycloalkenyl group;

R³ and R⁴ which may be the same or different, is each a hydrogen atom or an optionally substituted alkyl, -CO₂R⁷ (wherein R⁷ is a hydrogen atom, an optionally substituted alkyl, aralkyl, or aryl group) -CONR⁸R⁹ (wherein R⁸ and R⁹, which may be the same or different, is as defined for R⁷), -CSNR⁸R⁹, -CN or -CH₂CN group;

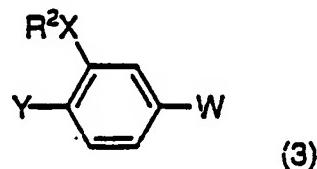
30

Z is -(CH₂)_n- where n is zero or an integer 1, 2 or 3;

R^5 is an optionally substituted monocyclic or bicyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms;
 and the salts, solvates, hydrates, prodrugs and N-oxides thereof,
 which comprises:

5

- i) reacting a compound of formula (3)



10

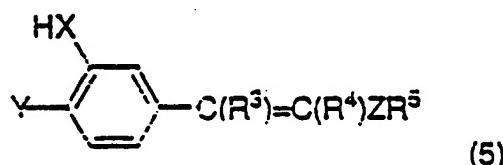
where

15

- (a) W is a $-C(O)R^3$ group, where R^3 is as defined for formula (1) but is not a $-CN$ or $-CH_2CN$ group, with a compound $R^5ZCH_2R^4$; or where
- (b) W is a $-CH_2R^3$ group with an aldehyde or ketone R^5ZCOR^4 , where R^4 is as just defined for R^3 ; or where
- (c) W is a $-C(O)R^3$ group with a silane derivative $Alk_3SiCH(R^4)(R^5)$ (where Alk is an alkyl group)
 in the presence of a base or an acid;

20

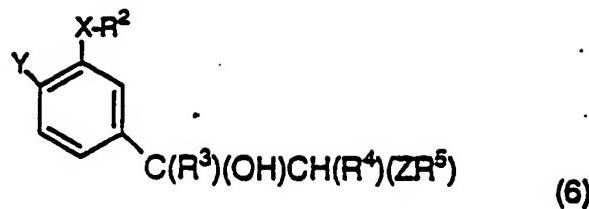
- ii) alkylating a compound of formula (5)



25

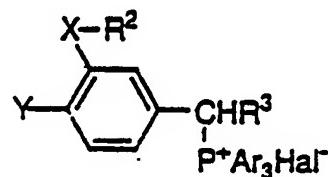
with a halide R^2Hal , or with an alcohol R^2OH ;

- iii) dehydrating an alcohol of formula (6)



using an acid at an elevated temperature;

- 5 iv) reacting a phosphonium salt



10 where Ar is an aryl group and Hal is a halogen atom with a compound R^5ZCOR^4; or

- v) interconverting a compound of formula (1) to yield another compound of formula (1).

15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 94/00452

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9200968	23-01-92	AU-A- 8229291	04-02-92
		CA-A- 2086741	11-01-92
		EP-A- 0538384	28-04-93
		JP-T- 6501679	24-02-94
		CN-A- 1060652	29-04-92